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(54) Fullerene derivatives as free-radical scavengers

(57) The invention relates to fullerene derivatives which are capable of scavenging free radicals. The derivatives have the formula $F(-X)_m(-Y-Z)_n$, in which F is a fullerene core; each X is independently $-\text{CO}_2^-$, $-\text{SO}_3^-$, $-\text{SH}$, or the like; each $-Y-Z$ is independently $(\text{C}_{3-30}$ alkyl

ether) $_{50}-\text{CH}_2-\text{CO}_2^-$, $(\text{C}_{3-30}$ alkyl ester) $_{50}-\text{CH}_2-\text{SO}_3^-$, $(\text{C}_{3-30}$ alkyl amide) $_{50}-\text{CH}_2-\text{SH}$, or the like; m is 0-30; n is 0-30; and the sum of m and n is 2-30.

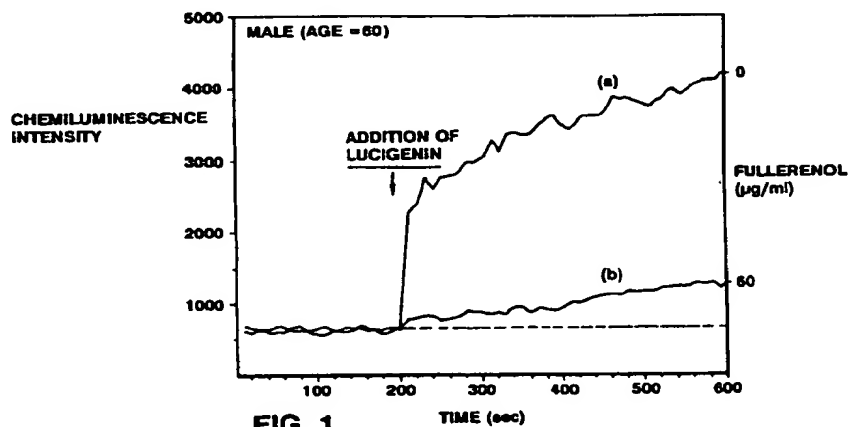


FIG. 1

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Description

Background of the Invention

Conjugated caged olefins, such as C₆₀ and analogous molecules thereof, have been found to be extraordinarily susceptible to the attack of a variety of chemical reagents. Particularly, they all exhibit high reactivity toward multiple additions of organic free radicals. This reactivity is, presumably, correlated to the intrinsically large electronegativity of such molecules.

Several functionalised fullerene derivatives have been reported for the biochemical or medical related studies. For example, bis (phenethylamino-succinate) C₆₀ inhibited the HIV-1 protease. Friedman, et al., J. Am. Chem. Soc. 1993, 115, 6506. As another example, photoactivated water-compatible monofunctionalized C₆₀ showed DNA-cleaving activity and in vitro cytotoxicity against the HeLa S3 cell line. Tokuyama, et al., J. Am. Chem. Soc. 1993, 115, 7918. Both activities were eliminated in the absence of a light source.

Summary of the Invention

The present invention relates to fullerene derivatives which, like the parent fullerenes, are capable of scavenging free radicals, but have reduced or no biological toxicity.

Viewed from one aspect the invention provides a compound of formula I:



wherein

F is a fullerene core;

each X is independently -CO₂⁻, -SO₃⁻, -OH, -SH, -PO₃⁻, -O-PO₃²⁻, -O-PO(O⁻)-O-PO₃²⁻, -O-PO(O⁻)-O-PO(O⁻)-O-PO₃²⁻, -O-PO(O⁻)-O-CH₂-CH₂-NH₃⁺, -NH₂, NH₃⁺, -N⁺H₂R_a, N⁺HR_aR_b or -N⁺R_aR_bR_c;

each Y is -A-B-, in which A is independently -CH₂-, -O-, -S-, -NH-CO-NH-, or -NH-CO-; and B is independently -R_d-O-[Si(CH₃)₂-O]₁₋₁₀₀, C₁₋₂₀₀₀ alkyl (a divalent radical), C₆₋₄₀ aryl (a divalent radical), C₇₋₆₀ alkylaryl (a divalent radical), C₇₋₆₀ arylalkyl (a divalent radical), (C₁₋₃₀ alkyl ether)₁₋₁₀₀, (C₆₋₄₀ aryl ether)₁₋₁₀₀, (C₇₋₆₀ alkylaryl ether)₁₋₁₀₀, (C₇₋₆₀ arylalkyl ether)₁₋₁₀₀, (C₁₋₃₀ alkyl thioether)₁₋₁₀₀, (C₆₋₄₀ aryl thioether)₁₋₁₀₀, (C₇₋₆₀ alkylaryl thioether)₁₋₁₀₀, (C₇₋₆₀ arylalkyl thioether)₁₋₁₀₀, (C₂₋₅₀ alkyl ester)₁₋₁₀₀, (C₇₋₆₀ aryl ester)₁₋₁₀₀, (C₈₋₇₀ alkylaryl ester)₁₋₁₀₀, (C₈₋₇₀ arylalkyl ester)₁₋₁₀₀, -R-CO-O-(C₁₋₃₀ alkyl ether)₁₋₁₀₀, -R-CO-O-(C₆₋₄₀ aryl ether)₁₋₁₀₀, -R-CO-O-(C₇₋₆₀ alkylaryl ether)₁₋₁₀₀, -R-CO-O-(C₇₋₆₀ arylalkyl ether)₁₋₁₀₀, (C₄₋₅₀ alkyl urethane)₁₋₁₀₀, (C₁₄₋₆₀ aryl urethane)₁₋₁₀₀, (C₁₀₋₈₀ alkylaryl urethane)₁₋₁₀₀, (C₁₀₋₈₀ arylalkyl urethane)₁₋₁₀₀, (C₅₋₅₀ alkyl urea)₁₋₁₀₀, (C₁₄₋₆₀ aryl urea)₁₋₁₀₀, (C₁₀₋₈₀ alkylaryl urea)₁₋₁₀₀, (C₁₀₋₈₀ arylalkyl urea)₁₋₁₀₀, (C₂₋₅₀ alkyl amide)₁₋₁₀₀, (C₇₋₆₀ aryl amide)₁₋₁₀₀, (C₈₋₇₀ alkylaryl amide)₁₋₁₀₀, (C₈₋₇₀ arylalkyl amide)₁₋₁₀₀, (C₃₋₃₀ alkyl anhydride)₁₋₁₀₀, (C₈₋₅₀ aryl anhydride)₁₋₁₀₀, (C₉₋₆₀ alkylaryl anhydride)₁₋₁₀₀, (C₉₋₆₀ arylalkyl anhydride)₁₋₁₀₀, (C₂₋₃₀ alkyl carbonate)₁₋₁₀₀, (C₇₋₅₀ aryl carbonate)₁₋₁₀₀, (C₈₋₆₀ alkylaryl carbonate)₁₋₁₀₀, (C₈₋₆₀ arylalkyl carbonate)₁₋₁₀₀, -R₁-O-CO-NH-(R₂ or Ar-R₂-Ar)-NH-CO-O-(C₁₋₃₀ alkyl ether, C₆₋₄₀ aryl ether, C₇₋₆₀ alkylaryl ether, or C₇₋₆₀ arylalkyl ether)₁₋₁₀₀, -R₁-O-CO-NH-(R₂ or Ar-R₂-Ar)-NH-CO-O-(C₂₋₅₀ alkyl ester, C₇₋₆₀ aryl ester, C₈₋₇₀ alkylaryl ester, or C₈₋₇₀ arylalkyl ester)₁₋₁₀₀, -R₁-O-CO-NH-(R₂ or Ar-R₂-Ar)-NH-CO-O-(C₁₋₃₀ alkyl ether, C₆₋₄₀ aryl ether, C₇₋₆₀ alkylaryl ether, or C₇₋₆₀ arylalkyl ether)₁₋₁₀₀, -CO-NH-(R₂ or Ar-R₂-Ar)-NH-CO-O-, -R₁-O-CO-NH-(R₂ or Ar-R₂-Ar)-NH-CO-O-(C₂₋₅₀ alkyl ester, C₇₋₆₀ aryl ester, C₈₋₇₀ alkylaryl ester, or C₈₋₇₀ arylalkyl ester)₁₋₁₀₀, -R₃-O-CO-NH-(R₂ or Ar-R₂-Ar)-NH-CO-O-, -R₁-NH-CO-NH-(R₂ or Ar-R₂-Ar)-NH-CO-O-(C₁₋₃₀ alkyl ether, C₆₋₄₀ aryl ether, C₇₋₆₀ alkylaryl ether, or C₇₋₆₀ arylalkyl ether)₁₋₁₀₀, -R₁-NH-CO-NH-(R₂ or Ar-R₂-Ar)-NH-CO-O-(C₂₋₅₀ alkyl ester, C₇₋₆₀ aryl ester, C₈₋₇₀ alkylaryl ester, or C₈₋₇₀ arylalkyl ester)₁₋₁₀₀, -R₁-NH-CO-NH-(R₂ or Ar-R₂-Ar)-NH-CO-O-(C₁₋₃₀ alkyl ether, C₆₋₄₀ aryl ether, C₇₋₆₀ alkylaryl ether, or C₇₋₆₀ arylalkyl ether)₁₋₁₀₀, -CO-NH-(R₂ or Ar-R₂-Ar)-NH-CO-O-, -R₁-NH-CO-NH-(R₂ or Ar-R₂-Ar)-NH-CO-O-(C₂₋₅₀ alkyl ester, C₇₋₆₀ aryl ester, C₈₋₇₀ alkylaryl ester, or C₈₋₇₀ arylalkyl ester)₁₋₁₀₀, -R₃-O-CO-NH-(R₂ or Ar-R₂-Ar)-NH-CO-O-, -R₁-O-CO-NH-(R₂ or Ar-R₂-Ar)-NH-CO-NH- (C₂₋₅₀ alkyl amide, C₇₋₆₀ aryl amide, C₇₋₇₀ arylalkyl amide)₁₋₁₀₀, or -R₁-NH-CO-NH-(R₂ or Ar-R₂-Ar)-NH-CO-NH-(C₂₋₅₀ alkyl amide, C₇₋₆₀ aryl amide, C₇₋₇₀ arylalkyl amide, or C₇₋₇₀ arylalkyl amide)₁₋₁₀₀;

each Z is -C-D, wherein C is independently -R-, -R-Ar-, -Ar-, or -Ar-R-; and D is independently -OH, -SH, -SO₃⁻, -OSO₃⁻, -CO₂⁻, -PO₃⁻, -O-PO₃²⁻, -O-PO(O⁻)-O-PO₃²⁻, -O-PO(O⁻)-O-PO(O⁻)-O-PO₃²⁻, -O-PO(O⁻)-O-CH₂-CH₂-NH₃⁺, -NH₂, NH₃⁺, -N⁺H₂R_a, N⁺HR_aR_b or -N⁺R_aR_bR_c; and

m is 0-30 (e.g. 0 or 0-16), n is 0-30 (e.g. 0-16, 4-16, or 2-30) and the sum of m and n is 2-30 (e.g. 4-16) with the proviso that where X is -OH, -NH₂, NH₃⁺, -N⁺H₂R_a, N⁺HR_aR_b or -N⁺R_aR_bR_c then n is at least 1;

in which each of R, R₁, R₂, R₃, R_a, R_b, R_c, R_d, R_a['], R_b['], and R_c['] is independently C₁₋₂₀ alkyl, and Ar is independently C₆₋₄₀ aryl (e.g. p-phenylene abbreviated as Ph herein), or a salt thereof.

Viewed from a further aspect the invention provides a composition comprising biologically compatible substance

and a compound of the formula I :



5 wherein

F is a fullerene core;

each X is independently $-\text{CO}_2^-$, $-\text{SO}_3^-$, $-\text{OH}$, $-\text{SH}$, $-\text{PO}_3^-$, $-\text{O}-\text{PO}_3^{2-}$, $-\text{O}-\text{PO}(\text{O}^-)-\text{O}-\text{PO}_3^{2-}$, $-\text{O}-\text{PO}(\text{O}^-)-\text{O}-\text{PO}(\text{O}^-)-\text{O}-\text{PO}_3^{2-}$, $-\text{O}-\text{PO}(\text{O}^-)-\text{O}-\text{CH}_2-\text{CH}_2-\text{NH}_3^+$, $-\text{NH}_2$, NH_3^+ , $-\text{N}^+\text{H}_2\text{R}_a$, $\text{N}^+\text{HR}_a\text{R}_b$ or $-\text{N}^+\text{R}_a\text{R}_b\text{R}_c$;

each Y is $-\text{A}-\text{B}-$, in which A is independently $-\text{CH}_2-$, $-\text{O}-$, $-\text{S}-$, $-\text{NH}-\text{CO}-\text{NH}-$, or $-\text{NH}-\text{CO}-$; and B is independently

10 $-\text{R}_d-\text{O}-[\text{Si}(\text{CH}_3)_2-\text{O}]_{1-100}$, C_{1-2000} alkyl (a divalent radical), C_{6-40} aryl (a divalent radical), C_{7-60} alkylaryl (a divalent radical), C_{7-60} arylalkyl (a divalent radical), $(\text{C}_{1-30}$ alkyl ether) $_{1-100}$, $(\text{C}_{6-40}$ aryl ether) $_{1-100}$, $(\text{C}_{7-60}$ alkylaryl ether) $_{1-100}$, $(\text{C}_{7-60}$ arylalkyl ether) $_{1-100}$, $(\text{C}_{1-30}$ alkyl thioether) $_{1-100}$, $(\text{C}_{6-40}$ aryl thioether) $_{1-100}$, $(\text{C}_{7-60}$ alkylaryl thioether) $_{1-100}$, $(\text{C}_{7-60}$ arylalkyl thioether) $_{1-100}$, $(\text{C}_{2-50}$ alkyl ester) $_{1-100}$, $(\text{C}_{7-60}$ aryl ester) $_{1-100}$, $(\text{C}_{8-70}$ alkylaryl ester) $_{1-100}$, $(\text{C}_{8-70}$ arylalkyl ester) $_{1-100}$, $-\text{R}-\text{CO}-\text{O}-$
15 $(\text{C}_{1-30}$ alkyl ether) $_{1-100}$, $-\text{R}-\text{CO}-\text{O}-$ $(\text{C}_{6-40}$ aryl ether) $_{1-100}$, $-\text{R}-\text{CO}-\text{O}-$ $(\text{C}_{7-60}$ alkylaryl ether) $_{1-100}$, $-\text{R}-\text{CO}-\text{O}-$ $(\text{C}_{7-60}$ arylalkyl ether) $_{1-100}$, $(\text{C}_{4-50}$ alkyl urethane) $_{1-100}$, $(\text{C}_{14-60}$ aryl urethane) $_{1-100}$, $(\text{C}_{10-80}$ alkylaryl urethane) $_{1-100}$, $(\text{C}_{10-80}$ arylalkyl urethane) $_{1-100}$, $(\text{C}_{5-50}$ alkyl urea) $_{1-100}$, $(\text{C}_{14-60}$ aryl urea) $_{1-100}$, $(\text{C}_{10-80}$ alkylaryl urea) $_{1-100}$, $(\text{C}_{10-80}$ arylalkyl urea) $_{1-100}$, $(\text{C}_{2-50}$ alkyl amide) $_{1-100}$, $(\text{C}_{7-60}$ aryl amide) $_{1-100}$, $(\text{C}_{8-70}$ alkylaryl amide) $_{1-100}$, $(\text{C}_{8-70}$ arylalkyl amide) $_{1-100}$, $(\text{C}_{3-30}$ alkyl anhydride) $_{1-100}$, $(\text{C}_{8-50}$ aryl anhydride) $_{1-100}$, $(\text{C}_{9-60}$ alkylaryl anhydride) $_{1-100}$, $(\text{C}_{9-60}$ arylalkyl anhydride) $_{1-100}$, $(\text{C}_{2-30}$ alkyl carbonate) $_{1-100}$, $(\text{C}_{7-50}$ aryl carbonate) $_{1-100}$, $(\text{C}_{8-60}$ alkylaryl carbonate) $_{1-100}$, $(\text{C}_{8-60}$ arylalkyl carbonate) $_{1-100}$, $-\text{R}_1-\text{O}-\text{CO}-\text{NH}-$
20 $(\text{R}_2 \text{ or Ar-R}_2\text{-Ar})-\text{NH}-\text{CO}-\text{O}-$ $(\text{C}_{1-30}$ alkyl ether) $_{1-100}$, $-\text{R}_1-\text{O}-\text{CO}-\text{NH}-$ $(\text{R}_2 \text{ or Ar-R}_2\text{-Ar})-\text{NH}-\text{CO}-\text{O}-$ $(\text{C}_{2-50}$ alkyl ester) $_{1-100}$, $-\text{R}_1-\text{O}-\text{CO}-\text{NH}-$ $(\text{R}_2 \text{ or Ar-R}_2\text{-Ar})-\text{NH}-\text{CO}-\text{O}-$ $(\text{C}_{7-60}$ aryl ester) $_{1-100}$, $-\text{R}_1-\text{O}-\text{CO}-\text{NH}-$ $(\text{R}_2 \text{ or Ar-R}_2\text{-Ar})-\text{NH}-\text{CO}-\text{O}-$ $(\text{C}_{8-70}$ alkylaryl ester) $_{1-100}$, $-\text{R}_1-\text{O}-\text{CO}-\text{NH}-$ $(\text{R}_2 \text{ or Ar-R}_2\text{-Ar})-\text{NH}-\text{CO}-\text{O}-$ $(\text{C}_{8-70}$ arylalkyl ester) $_{1-100}$, $-\text{CO}-\text{NH}-$ $(\text{R}_2 \text{ or Ar-R}_2\text{-Ar})-\text{NH}-\text{CO}-\text{O}-$, $-\text{R}_1-\text{O}-\text{CO}-\text{NH}-$ $(\text{R}_2 \text{ or Ar-R}_2\text{-Ar})-\text{NH}-\text{CO}-\text{O}-$
25 $(\text{C}_{2-50}$ alkyl ester) $_{1-100}$, $-\text{R}_1-\text{NH}-\text{CO}-\text{NH}-$ $(\text{R}_2 \text{ or Ar-R}_2\text{-Ar})-\text{NH}-\text{CO}-\text{O}-$ $(\text{C}_{1-30}$ alkyl ether) $_{1-100}$, $-\text{R}_1-\text{NH}-\text{CO}-\text{NH}-$ $(\text{R}_2 \text{ or Ar-R}_2\text{-Ar})-\text{NH}-\text{CO}-\text{O}-$ $(\text{C}_{2-50}$ alkyl ester) $_{1-100}$, $-\text{R}_1-\text{NH}-\text{CO}-\text{NH}-$ $(\text{R}_2 \text{ or Ar-R}_2\text{-Ar})-\text{NH}-\text{CO}-\text{O}-$ $(\text{C}_{7-60}$ aryl ester) $_{1-100}$, $-\text{R}_1-\text{NH}-\text{CO}-\text{NH}-$ $(\text{R}_2 \text{ or Ar-R}_2\text{-Ar})-\text{NH}-\text{CO}-\text{O}-$ $(\text{C}_{8-70}$ alkylaryl ester) $_{1-100}$, $-\text{R}_1-\text{NH}-\text{CO}-\text{NH}-$ $(\text{R}_2 \text{ or Ar-R}_2\text{-Ar})-\text{NH}-\text{CO}-\text{O}-$ $(\text{C}_{8-70}$ arylalkyl ester) $_{1-100}$, $-\text{R}_1-\text{NH}-\text{CO}-\text{NH}-$ $(\text{R}_2 \text{ or Ar-R}_2\text{-Ar})-\text{NH}-\text{CO}-\text{O}-$
30 $(\text{C}_{2-50}$ alkyl amide) $_{1-100}$, $-\text{R}_1-\text{O}-\text{CO}-\text{NH}-$ $(\text{R}_2 \text{ or Ar-R}_2\text{-Ar})-\text{NH}-\text{CO}-\text{NH}-$ $(\text{C}_{2-50}$ alkyl amide) $_{1-100}$, $-\text{R}_1-\text{O}-\text{CO}-\text{NH}-$ $(\text{R}_2 \text{ or Ar-R}_2\text{-Ar})-\text{NH}-\text{CO}-\text{NH}-$ $(\text{C}_{7-60}$ aryl amide) $_{1-100}$, $-\text{R}_1-\text{O}-\text{CO}-\text{NH}-$ $(\text{R}_2 \text{ or Ar-R}_2\text{-Ar})-\text{NH}-\text{CO}-\text{NH}-$ $(\text{C}_{8-70}$ alkylaryl amide) $_{1-100}$, $-\text{R}_1-\text{O}-\text{CO}-\text{NH}-$ $(\text{R}_2 \text{ or Ar-R}_2\text{-Ar})-\text{NH}-\text{CO}-\text{NH}-$ $(\text{C}_{8-70}$ arylalkyl amide) $_{1-100}$;

each Z is $-\text{C}-\text{D}$, wherein C is independently $-\text{R}-$, $-\text{R}-\text{Ar}-$, $-\text{Ar}-$, or $-\text{Ar}-\text{R}-$; and D is independently $-\text{OH}$, $-\text{SH}$, $-\text{SO}_3^-$, $-\text{OSO}_3^-$, $-\text{CO}_2^-$, $-\text{PO}_3^-$, $-\text{O}-\text{PO}_3^{2-}$, $-\text{O}-\text{PO}(\text{O}^-)-\text{O}-\text{PO}_3^{2-}$, $-\text{O}-\text{PO}(\text{O}^-)-\text{O}-\text{PO}(\text{O}^-)-\text{O}-\text{PO}_3^{2-}$, $-\text{O}-\text{PO}(\text{O}^-)-\text{O}-\text{CH}_2-\text{CH}_2-\text{NH}_3^+$, $-\text{NH}_2$, $-\text{NH}_3^+$, $-\text{N}^+\text{H}_2\text{R}_a$, $\text{N}^+\text{HR}_a\text{R}_b$ or $-\text{N}^+\text{R}_a\text{R}_b\text{R}_c$; and

35 m is 0-30 (e.g. 1-16 or 1-12), n is 0-30 (e.g. 0-16, or 0-12) and the sum of m and n is 2-30 (e.g. 4-16 or 6-12); in which each of R , R_1 , R_2 , R_3 , R_a , R_b , R_c , R_d , R_a , R_b and R_c is independently C_{1-20} alkyl, and Ar is independently C_{6-40} aryl, or a salt thereof.

Conveniently, in the compound of formula I,

40 each X is independently $-\text{CO}_2^-$, $-\text{SO}_3^-$, $-\text{SH}$, $-\text{PO}_3^-$, $-\text{O}-\text{PO}_3^{2-}$, $-\text{O}-\text{PO}(\text{O}^-)-\text{O}-\text{PO}_3^{2-}$, $-\text{O}-\text{PO}(\text{O}^-)-\text{O}-\text{PO}(\text{O}^-)-\text{O}-\text{PO}_3^{2-}$, $-\text{O}-\text{PO}(\text{O}^-)-\text{O}-\text{CH}_2-\text{CH}_2-\text{NH}_3^+$,

each B is independently $-\text{R}_d-\text{O}-[\text{Si}(\text{CH}_3)_2-\text{O}]_{1-100}$, C_{1-2000} alkyl, C_{6-40} aryl, C_{7-60} alkylaryl, C_{7-60} arylalkyl, $(\text{C}_{1-30}$ alkyl ether) $_{1-100}$, $(\text{C}_{7-60}$ alkylaryl ether) $_{1-100}$, $(\text{C}_{1-30}$ alkyl thioether) $_{1-100}$, $(\text{C}_{7-60}$ alkylaryl thioether) $_{1-100}$, $(\text{C}_{2-50}$ alkyl ester) $_{1-100}$, $(\text{C}_{8-70}$ alkylaryl ester) $_{1-100}$, $-\text{R}-\text{CO}-\text{O}-$
45 $(\text{C}_{1-30}$ alkyl ether) $_{1-100}$, $(\text{C}_{4-50}$ alkyl urethane) $_{1-100}$, $(\text{C}_{10-80}$ alkylaryl urethane) $_{1-100}$, $(\text{C}_{5-50}$ alkyl urea) $_{1-100}$, $(\text{C}_{10-80}$ alkylaryl urea) $_{1-100}$, $(\text{C}_{2-50}$ alkyl amide) $_{1-100}$, $(\text{C}_{8-70}$ alkylaryl amide) $_{1-100}$, $(\text{C}_{3-30}$ alkyl anhydride) $_{1-100}$, $(\text{C}_{9-60}$ alkylaryl anhydride) $_{1-100}$, $(\text{C}_{2-30}$ alkyl carbonate) $_{1-100}$, $(\text{C}_{8-60}$ alkylaryl carbonate) $_{1-100}$, $-\text{R}_1-\text{O}-\text{CO}-\text{NH}-$ $(\text{R}_2 \text{ or Ph-R}_2\text{-Ph})-\text{NH}-\text{CO}-\text{O}-$ $(\text{C}_{1-30}$ alkyl ether) $_{1-100}$, $-\text{R}_1-\text{O}-\text{CO}-\text{NH}-$ $(\text{R}_2 \text{ or Ph-R}_2\text{-Ph})-\text{NH}-\text{CO}-\text{O}-$ $(\text{C}_{2-50}$ alkyl ester) $_{1-100}$, $-\text{R}_1-\text{O}-\text{CO}-\text{NH}-$ $(\text{R}_2 \text{ or Ph-R}_2\text{-Ph})-\text{NH}-\text{CO}-\text{O}-$ $(\text{C}_{7-60}$ alkylaryl ester) $_{1-100}$, $-\text{R}_1-\text{O}-\text{CO}-\text{NH}-$ $(\text{R}_2 \text{ or Ph-R}_2\text{-Ph})-\text{NH}-\text{CO}-\text{O}-$ $(\text{C}_{8-70}$ alkylaryl ester) $_{1-100}$, $-\text{CO}-\text{NH}-$ $(\text{R}_2 \text{ or Ph-R}_2\text{-Ph})-\text{NH}-\text{CO}-\text{O}-$, $-\text{R}_1-\text{NH}-\text{CO}-\text{NH}-$ $(\text{R}_2 \text{ or Ph-R}_2\text{-Ph})-\text{NH}-\text{CO}-\text{O}-$, $-\text{R}_1-\text{NH}-\text{CO}-\text{NH}-$ $(\text{R}_2 \text{ or Ph-R}_2\text{-Ph})-\text{NH}-\text{CO}-\text{O}-$
50 $(\text{C}_{1-30}$ alkyl ether) $_{1-100}$, $-\text{R}_1-\text{NH}-\text{CO}-\text{NH}-$ $(\text{R}_2 \text{ or Ph-R}_2\text{-Ph})-\text{NH}-\text{CO}-\text{O}-$ $(\text{C}_{2-50}$ alkyl ester) $_{1-100}$, $-\text{R}_1-\text{NH}-\text{CO}-\text{NH}-$ $(\text{R}_2 \text{ or Ph-R}_2\text{-Ph})-\text{NH}-\text{CO}-\text{O}-$ $(\text{C}_{7-60}$ alkylaryl ester) $_{1-100}$, $-\text{R}_1-\text{NH}-\text{CO}-\text{NH}-$ $(\text{R}_2 \text{ or Ph-R}_2\text{-Ph})-\text{NH}-\text{CO}-\text{O}-$ $(\text{C}_{8-70}$ alkylaryl ester) $_{1-100}$, $-\text{CO}-\text{NH}-$ $(\text{R}_2 \text{ or Ph-R}_2\text{-Ph})-\text{NH}-\text{CO}-\text{O}-$, $-\text{R}_1-\text{O}-\text{CO}-\text{NH}-$ $(\text{R}_2 \text{ or Ph-R}_2\text{-Ph})-\text{NH}-\text{CO}-\text{NH}-$ $(\text{C}_{2-50}$ alkyl amide) $_{1-100}$, $-\text{R}_1-\text{O}-\text{CO}-\text{NH}-$ $(\text{R}_2 \text{ or Ph-R}_2\text{-Ph})-\text{NH}-\text{CO}-\text{NH}-$ $(\text{C}_{7-60}$ alkylaryl amide) $_{1-100}$, or $-\text{R}_1-\text{NH}-\text{CO}-\text{NH}-$ $(\text{R}_2 \text{ or Ph-R}_2\text{-Ph})-\text{NH}-\text{CO}-\text{NH}-$ $(\text{C}_{2-50}$ alkyl amide) $_{1-100}$, $-\text{R}_1-\text{O}-\text{CO}-\text{NH}-$ $(\text{R}_2 \text{ or Ph-R}_2\text{-Ph})-\text{NH}-\text{CO}-\text{NH}-$ $(\text{C}_{8-70}$ alkylaryl amide) $_{1-100}$;

and each C is independently $-\text{R}-$, $-\text{R}-\text{Ph}$ in which Ph is p-phenylene; and

55 each D is independently $-\text{SO}_3^-$, $-\text{OSO}_3^-$, $-\text{CO}_2^-$, $-\text{PO}_3^-$, $-\text{O}-\text{PO}_3^{2-}$, $-\text{O}-\text{PO}(\text{O}^-)-\text{O}-\text{PO}_3^{2-}$, $-\text{O}-\text{PO}(\text{O}^-)-\text{O}-\text{PO}(\text{O}^-)-\text{O}-\text{PO}_3^{2-}$, $-\text{O}-\text{PO}(\text{O}^-)-\text{O}-\text{CH}_2-\text{CH}_2-\text{NH}_3^+$, or a salt thereof.

What is meant by "a biologically compatible substance" is a substance other than water which has no toxicity and is intended to be ingested by or otherwise brought into contact with human bodies, e.g. a substance that is contained in a pharmaceutical (drug or vitamin) product, a cosmetic product, a skin-care product, a food product, or a cigarette.

Examples of compositions of this invention include, but are not limited to, a pharmaceutical formulation containing a free-radical scavenging fullerene derivative and an excipient, and a cigarette filter with a free-radical scavenging fullerene derivative covalently or non-covalently dispersed in it.

What is meant by "fullerene core" is a caged molecule consisting essentially of carbon atoms such as C_{60} , $C_{60}H_x$, C_{61} , C_{62} , C_{71} , C_{72} , $C_{60}O_x$, $C_{60}N_x$, $C_{61}O_x$, $C_{62}O_x$, $C_{70}O_x$, $C_{71}O_x$, $C_{72}O_x$, $C_{70}N_x$, C_{76} , $C_{76}O_x$, C_{78} , $C_{78}O_x$, C_{82} , $C_{82}O_x$, C_{84} , $C_{84}O_x$, C_{92} , $C_{92}O_x$, and the like, in which x is 1-20 (e.g. 1-8). $C_{60}O_x(OH)_y$ is an example of a fullerene derivative in which $C_{60}O_x$ is the fullerene core with hydroxyl groups linked to it. $C_{60}H_x(NRR')_x$ on the other hand, is an example where $C_{60}H_x$ is the fullerene cage.

The structures of many of the moieties mentioned above are shown below within the pair of parentheses following each of the moieties: alkyl ether (-R-O-), aryl ether (-Ar-O-), alkylaryl ether (-R-Ar-O-), arylalkyl ether (-Ar-R-O-), alkyl thioether (-R-S-), aryl thioether (-Ar-S-), alkylaryl thioether (-R-Ar-S-), arylalkyl thioether (-Ar-R-S-), alkyl ester (-R-O-CO-, -R-CO-O-, -R₁-CO-O-R₂-O-CO-, or -R₁-O-CO-R₂-CO-O-), aryl ester (-Ar-O-CO-, -Ar-CO-O-, -Ar₁-CO-O-Ar₂-O-CO-, or -Ar₁-O-CO-Ar₂-CO-O-), alkylaryl ester (-R-Ar-O-CO- or -R-Ar-CO-O-), arylalkyl ester (-Ar-R-CO-O- or -Ar-R-CO-O-), alkyl urethane (-R₁-O-CO-NH-R₂-NH-CO-O-), aryl urethane (-Ar₁-O-CO-NH-Ar₂-NH-CO-O-), alkylaryl urethane (-R₁-Ar-O-CO-NH-R₂-NH-CO-O-, -R-Ar₁-O-CO-NH-Ar₂-NH-CO-O-, or -R₁-O-CO-NH-Ar₂-Ar-NH-CO-O-), arylalkyl urethane (-Ar-R₁-O-CO-NH-R₂-NH-CO-O-, -Ar₁-R-O-CO-NH-Ar₂-NH-CO-O-, or -Ar₁-O-CO-NH-Ar₂-R-Ar₂-NH-CO-O-), alkyl urea (-R₁-NH-CO-NH-R₂-NH-CO-NH-), aryl urea (-Ar₁-NH-CO-NH-Ar₂-NH-CO-NH-), alkylaryl urea (-R₁-Ar-NH-CO-NH-R₂-NH-CO-NH-, -R-Ar₁-NH-CO-NH-Ar₂-NH-CO-NH-, or -R₁-NH-CO-NH-Ar₂-Ar-NH-CO-NH-), arylalkyl urea (-Ar-R₁-NH-CO-NH-R₂-NH-CO-NH-, -Ar₁-R-NH-CO-NH-Ar₂-NH-CO-NH-, or -Ar₁-NH-CO-NH-Ar₂-R-Ar₂-NH-CO-NH-), alkyl amide (-R-NH-CO-, -R-CO-NH-, -R₁-CO-NH-R₂-NH-CO-, or -R₁-NH-CO-R₂-CO-NH-), aryl amide (-Ar-NH-CO-, -Ar-CO-NH-, -Ar₁-CO-NH-Ar₂-NH-CO-, or -Ar₁-NH-CO-Ar₂-CO-NH-), alkylaryl amide (-R-Ar-NH-CO-, -R-CO-NH-Ar-NH-CO-, or -R-NH-CO-Ar-CO-NH-), arylalkyl amide (-Ar-R-NH-CO-, -Ar-CO-NH-R-NH-CO-, or -Ar-NH-CO-R-CO-NH-), alkyl anhydride (-R-CO-O-CO-), aryl anhydride (-Ar-CO-O-CO-), alkylaryl anhydride (-R-Ar-CO-O-CO- or -R-CO-O-CO-Ar-CO-O-CO-), arylalkyl anhydride (-Ar-R-CO-O-CO- or -Ar-CO-O-CO-R-CO-O-CO-), alkyl carbonate (-R-O-CO-O-), aryl carbonate (-Ar-O-CO-O-), alkylaryl carbonate (-R-Ar-O-CO-O- or -E-O-CO-O-Ar-O-CO-O-), and arylalkyl carbonate (-Ar-R-O-CO-O- or -Ar-O-CO-O-R-O-CO-O-). Note that the symbols R, R₁, R₂, and Ar used in this paragraph do not necessarily have the same carbon numbers as the same symbols used elsewhere in this disclosure.

One can use fullerene derivatives described herein to detect free radicals in the blood of a patient in a manner identical or analogous to that shown in Example 18 below. Alternatively, such fullerene derivatives can be used as free-radical scavenging agents in a cigarette filter or in a device attached to a cigarette for absorbing gas phase reactive free radicals, especially radicals such as NO and NO₂ generated from the combustion of tobacco leaves. They can also be used as antioxidant additives in food products, as substitutes for vitamin C, as anti-ageing agents in skin-care lotions and cosmetic products. Clinic applications include: reducing free radicals in ischemia reperfusion injuries; inhibiting tissue and cell damages induced by acute pancreatitis, various cancers (e.g., gastric cancer, breast cancer, or ovarian cancer), and other free-radical related diseases such as diabetes and neurodegenerative diseases (e.g. Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis); suppressing proliferation of cancer cells and smooth muscle cells (e.g. as in atherosclerosis and restenosis). Indeed, more and more injuries and diseases have been found to be linked to free radical-mediated disturbances.

Thus, viewed from a still further aspect the invention provides (1) A compound of formula I or a salt thereof as hereinbefore described for medical use (2) The use of compound of formula I or a salt thereof as hereinbefore described for the manufacture of a medicament for the treatment of disorders or diseases associated with free radicals.

The dose of a pharmaceutical composition of this invention varies depending upon the manner of administration, the age and the body weight of the subject and the condition of the subject to be treated, and ultimately will be decided by the attending physician or veterinarian. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient(s) into association with the carrier which constitutes one or more accessory ingredients. In general, the formulations for tablets or powders are prepared by uniformly and intimately blending the active ingredient with finely divided solid carriers, and then, if necessary as in the case of tablets, forming the product into the desired shape and size.

Other features or advantages of the present invention will be apparent from the following drawings and detailed description of several embodiments, and also from the appending claims.

Brief Description of the Drawings

The drawings are first described.

Fig. 1 is a graph showing chemiluminescence intensity levels of whole blood from a male patient with acute pancreatitis: (a) no pretreatment with a fullerene; and (b) pretreatment with a fullerene.

Fig. 2 is a graph showing the effect of two fullerenes on the proliferative response of rabbit vascular smooth muscle

Detailed Description of the Invention

Described below are various methods for synthesizing the free-radical scavenging fullerene derivatives described herein.

Water-soluble polyhydroxylated fullerene derivatives, $C_{60}(OH)_x$ or polyoxy-hydroxylated fullerene derivatives, $C_{60}O_x(OH)_y$ can be prepared by one of the following six methods:

(a) Fullerenol-1 can be prepared from hydrolysis of the reaction products of fullerenes, either pure C_{60} or a mixture of C_{60} (84%) and C_{70} (16%), with nitronium tetrafluoroborate in the presence of organocarboxylic acid (RCO_2H) at ambient temperature. Chiang et al., U.S. Patent 5,177,248; Chiang et al. U.S. Patent 5,294,732; and Chiang et al., J. Am. Chem. Soc. 1992, 114, 10154; Chiang et al., J. Am. Chem. Soc. 1993, 115, 5453. The structure of fullerenol-1 has been characterized to consist of $C_{60}O_x(OH)_y$ with $x < 5$ and $y = 18$ on average.

(b) Fullerenol-2 can be synthesized via hydrolysis of the reaction products of fullerenes, either pure C_{60} or a mixture of C_{60} (85%) and C_{70} (16%), with a solution of sulfur trioxide (30%) in sulfuric acid. See Chiang et al., J. Org. Chem. 1994, 59, 3960. The structure of fullerenol-2 has been characterized to consist of $C_{60}(OH)_y$ with $y = 12$ on average.

(c) Fullerenol-3 can be prepared by the reaction of fullerenes with either a mixture of conc. H_2SO_4 , conc. HNO_3 and water at $90^\circ C$ or a mixture of oleum ($H_2SO_4 \cdot SO_3$), FNO_2 and water. See Chiang et al., U.S. Patent 5,177,248; Chiang et al. U.S. Patent 5,294,732; Chiang et al., J. Chem. Soc., Chem. Commun. 1992, 1791; Chiang, et al., Mat. Res. Soc. Symp. Proc. 1992, 247. The structure of fullerenol-3 has been characterized to consist of $C_{60}O_x(OH)_y$ with $x < 5$ and $y = 15$ on average.

(d) Fullerenol-4 can be synthesized by the reaction of fullerenes, dissolved in either benzene or toluene, with aqueous sodium hydroxide in the presence of a catalytic amount of tetrabutylammonium hydroxide and oxygen (in air). See Li et al., J. Chem. Soc., Chem. Commun. 1993, 1784. The structure of fullerenol-4 has been characterized to consist of polyhydroxylated C_{60} fullerene derivatives with 26 hydroxy groups per C_{60} cage on average.

(e) Fullerenol-5 can be prepared by the reaction of fullerenes, dissolved in either benzene or toluene, and gaseous nitrogen dioxide, followed by hydrolysis of resulting products with aqueous NaOH. See Chiang et al., Tetrahedron, "Efficient One-Flask Synthesis of Water-soluble [60]Fullerenols," in press. Gaseous nitrogen dioxide can be generated by either reacting $NaNO_2$ with $FeSO_4$ in aqueous H_2SO_4 in the presence of air (Roy, et al., J. Chem. Soc., Chem. Commun. 1994, 275) or reacting $NaNO_2$ with conc. HNO_3 . The former method yield nitrofullerenols consisting 6-8 nitro and 7-12 hydroxy groups per C_{60} . Hydrolysis of these products results in fullerenols with 13-20 hydroxy groups per C_{60} . The later method gives water-soluble fullerenols with a maximum number of hydroxy groups per C_{60} as 20 as identified by the FAB mass spectroscopy.

(f) Fullerenol-6 can be synthesized by the reaction of fullerenes with an excess of BH_3 -tetrahydrofuran (THF) complex followed by hydrolysis with either sodium hydroxide/hydrogen peroxide or sodium hydroxide. See Schneider, et al., J. Chem. Soc., Chem. Commun. 1994, 463.

Polyaminohydroxylated fullerene derivatives, $C_{60}(OH)_x(NH_2)_y$ or polyoxyaminohydroxylated fullerene derivatives, $C_{60}O_x(OH)_y(NH_2)_z$, can be prepared from hydrolysis of the reaction products of fullerenes, either pure C_{60} or a mixture of C_{60} (84%) and C_{70} (16%), with nitronium tetrafluoroborate in the presence of organocarbamide ($RCONH_2$) at ambient temperature. See Chiang et al., U.S. Patent 5,177,248; and Chiang, et al., U.S. Patent 5,294,732.

Dialkyl or diaryl methano-bridged fullerene derivatives, $C_{61}(R)_2$ or $C_{61}(-C_6H_5-R)_2$, can be synthesized by one the three following methods:

(a) Dialkyl or diaryl methano-bridged fullerene derivatives $C_{61}(R)_2$ or $C_{61}(-C_6H_5-R)_2$ can be prepared from the reaction of C_{60} fullerene with diazoalkanes or diphenyldiazomethane derivatives to give mono-addition of functionalized or non-functionalized diphenylmethane on C_{60} . See Suzuki, et al., Science 1991, 254, 1186; and Isaacs, et al., Helv. Chim. Acta 1993, 76, 1231.

(b) Dialkyl methano-bridged fullerene derivatives $C_{61}(R)_2$ can be prepared from the reaction of C_{60} fullerene with bromomalononic acid diethyl ester and sodium hydride to give mono-addition of malonic acid diethyl ester on C_{60} . See Paulus, et al., Acta Cryst. 1995, C51, 143.

(c) Alkyl methano-bridged fullerene derivatives $C_{61}(R)$ can be prepared from the reaction of C_{60} fullerene with 1-(4-methoxyphenyl)-1-(trimethylsilyloxy)ethylene to give the corresponding product of $C_{61}(COC_6H_4OMe)$. See Shu, et al., J. Chem. Soc., Chem. Commun. 1995, 367.

Polyalkyl fullerene derivatives, $C_{60}(R)_x$, can be synthesized by one of the two following methods:

(a) Polyalkyl fullerene derivatives can be synthesized by the reaction of fullerenes with organic alkyl radicals ($R \cdot$) to give products of $C_{60}(R)_x$ with $x = 1$ to at least 15. See Krusic, et al., Science 1991, 254, 1183.

(b) Polyalkyl fullerene derivatives can be synthesized by the reaction of fullerenes with organic alkyl lithium or alkyl

Grignard reagents (R^-) followed by reacting the resulting intermediates with alkyl halides to give products of $C_{60}(R)_x$ with $x = 1$ to 30. See Wudl, et al., ACS Symp. Ser. 1992, 481, 161.

Polyalkylamino fullerene derivatives, $C_{60}H_x(NRR')_x$, can be synthesized by the reaction of fullerenes with alkyl amine at ambient temperature for 2 days to give the corresponding products of $C_{60}H_x(NRR')_x$ with $x=6$ predominately. See Hirsch, et al, Angew. Chem. Int. Ed. Engl. 1991, 30, 1309.

Monocycloalkyl, monocycloaryl, polycycloalkyl, or polycycloaryl fullerene derivatives, $C_{60}(cyclo-R)$ or $C_{60}(cyclo-Ar)$ where x is 1-7, can be synthesized by one of the following four methods:

- (a) Monocycloaryl and polycycloaryl fullerene derivatives can be prepared by the reaction of fullerenes with benzyne to give products of $C_{60}(C_6H_4)_x$ with $x = 1-4$. See Hoke, et al., J. Org. Chem. 1992, 57, 5069; and Tsuda, et al., Chem. Lett. 1992, 2333.
- (b) Monocycloalkyl and polycycloalkyl fullerene derivatives can be synthesized by the reaction of fullerenes with enones via [2+2] photocycloaddition to give the corresponding fullerene products consisting with 1-7 enone adducts. See Wilson, et al., J. Am. Chem. Soc. 1993, 115, 8495.
- (c) Monocycloaryl and dicycloaryl fullerene derivatives were synthesized by the reaction of fullerenes with *o*-quinodimethane via [2+4] cycloaddition to give products of $C_{60}(-CH_2C_6H_4CH_2-)_x$ with $x = 1$ or 2. Belik, et al., Angew. Chem. Int. Ed. Engl. 1993, 32, 78.
- (d) Monocycloalkyl fullerene derivative can be synthesized by the reaction of C_{60} fullerene with 7-alkylidene-2,3-diazabicycloheptene via [2+3] cycloaddition to give the corresponding methylene-cyclopentane mono-adduct of fullerene, $C_{60}(-cyclopentene-CH_2-)$. See Prato, et al., J. Am. Chem. Soc. 1993, 115, 1594.

The radical-scavenging fullerene derivatives which are substituted with polymeric chains can be prepared by either one-step or multiple-step synthesis involving the reaction of a functional precursor at the connecting junction of each chain. For example, the ester connecting junction ($-O-CO-$) is performed by reacting an organic alcohol with an organic acid chloride or with an organic acid in the presence of a catalytic amount of Lewis acid. The urethane connecting junction ($-O-CO-NH-$) is performed by reacting an organic alcohol with an isocyanated organic compound. The urea connecting junction ($-NH-CO-NH-$) is performed by reacting an organic amine with an isocyanated organic compound. The amide ($-NH-CO-$) connecting junction is performed by reacting an organic amine with an organic acid chloride or with an organic acid in the presence of a catalytic amount of Lewis acid. The carbonate connecting junction ($-O-CO-O-$) is performed by reacting organic alcohols with phosgene ($Cl-CO-Cl$) in the presence of triethylamine. The anhydride connecting junction ($-CO-O-CO-$) is performed by reacting an organic acid with an organic acid chloride in the presence of triethylamine. Other precursors such as alkyls (alkanes, functional alkanes, and functional polyolefins), ethers (functional alkyl ether, functional aryl ether, functional alkylaryl ether, and functional arylalkyl ether), thioethers (functional alkyl thioether, functional aryl thioether, functional alkylaryl thioether, and functional arylalkyl thioether), and functional poly(dialkyl silicone oxide) are available commercially.

Fullerene derivatives containing mixed substituents chemically bonded onto a common fullerene cage can be synthesized in a stepwise manner by introducing a first group of substituents according to one of the methods described in Examples 1-19, isolating the resulting fullerene derivatives, protecting certain functionalities if necessary, and then introducing a second group of substituents according to one of the other methods described in Examples 1-19. As an example, poly(sodium sulfonylbutylated) fullerenes, $C_{60}(CH_2CH_2CH_2CH_2SO_3Na)_x$, are synthesized according to the method described in Example 9. They can then be hydroxylated by one of the methods described in Examples 1, 5, and 6, as well as methods (a)-(c) set forth above to afford the corresponding mixed-functional fullerenes $C_{60}(CH_2CH_2CH_2CH_2SO_3Na)_x(OH)_y$. Further conversion of hydroxy groups to urethanic groups can be carried out by the treatment of them with isocyanated organics, $OCN-B-C-D$ (B, C, and D being any of the moieties assigned to them respectively in the "Summary of the Invention" section) to give fullerene derivatives $C_{60}(CH_2CH_2CH_2CH_2SO_3Na)_x(O-CO-NH-B-C-D)_y$.

Examples 1-19 below provide other synthetic methods for preparing fullerene derivatives which are capable of scavenging free radicals. Examples 20-22, on the other hand, demonstrate some utilities of such fullerene-based compounds.

Without further elaboration, it is believed that one skilled in the art can, based on the description herein, utilize the present invention to its fullest extent. The following specific examples are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever. All publications recited above and in the examples are hereby incorporated by reference.

Example 1: Synthesis of water-soluble polyhydroxylated fullerene derivatives $C_{60}(OH)_x$ (fullerenol-7)

A reaction flask (100 ml) was charged with fullerenes (1.0 g), either pure C_{60} or a mixture of C_{60} and C_{70} , dissolved in toluene (50 ml) and an aqueous solution containing ammonium persulfate $((NH_4)_2S_2O_8$, 2.0 g), tetrabutylammonium

chloride (300 mg) or tricaprylylmethylammonium chloride (aliquat 336, 0.6 g), dibasic sodium phosphate (Na_2HPO_4 , 2.0 g), and distilled water (20 ml). The solution mixture was purged with N_2 for 10 min prior to heating at 80°C for 4-16 h. During the period of heating, the color of solution was observed to transfer from the toluene layer to the aqueous layer progressively with partially suspended brown solids as intermediates. At the end of reaction, the resulting mixture was added methanol (60 ml) to effect precipitation of brown solids. The solid precipitate was isolated by centrifugation. It was then washed twice with a mixture of methanol and H_2O (3:1, 30 ml each time) and dried in vacuum at 40°C to afford brown solids of polyhydroxylated fullerene derivatives $\text{C}_{60}(\text{OH})_x$ (850-950 mg, fullereneol-7). The number of hydroxy addends on the C_{60} cage increased upon the increase of heating period. The solubility of fullereneol-7 in water increased with the increase of the number of hydroxy addends. In general, fullereneol with less than 12 hydroxy groups has appreciable solubility in dimethylformamide (DMF). Further purification of fullereneol-7 was carried out by the rapid filtration of fullereneol-7 in H_2O -DMF solution through a column packed with Dowex ion exchange resins. Infrared data of fullereneol-7 are as follows: IR_{max} (KBr) 3450 (br, OH), 1615, 1403, 1107 and 578 cm^{-1} .

Example 2: Synthesis of water-soluble polyhydroxylated fullerene derivatives $\text{C}_{60}(\text{OH})_x$ (fullereneol-8)

A reaction flask (100 ml) was charged with fullerenes (1.0 g), either pure C_{60} or a mixture of C_{60} and C_{70} , dissolved in toluene (50 ml) and an aqueous solution containing iron (II) sulfate (FeSO_4 , 1.8 g), hydrogen peroxide (30% in H_2O , 10 ml), anionic surfactant such as sodium dodecylbenzenesulfonate (500 mg), and distilled water (20 ml). The solution mixture was purged with N_2 for 10 min prior to heating at 80°C for 4-16 h. During the period of heating, the color of solution was observed to transfer from the toluene layer to the aqueous layer progressively with partially suspended brown solids as intermediates. At the end of the reaction, the resulting mixture was added methanol (60 ml) to effect precipitation of brown solids. The solid precipitate was isolated by centrifugation. It was then washed twice with a mixture of methanol and H_2O (3:1, 30 ml each time) and dried in vacuum at 40°C to afford brown solids of polyhydroxylated fullerene derivatives $\text{C}_{60}(\text{OH})_x$ (900 mg, fullereneol-8). The number of hydroxy addends on the C_{60} cage increased upon the increase of heating period. The solubility of fullereneol-8 in water increased with the increase of the number of hydroxy addends. In general, fullereneol with less than 12 hydroxy groups has appreciable solubility in DMF. Further purification of fullereneol-8 was carried out by the rapid filtration of fullereneol-8 in H_2O -DMF solution through a column packed with Dowex ion exchange resins. Infrared data of fullereneol-8 are as follows: IR_{max} (KBr) 3450 (br, OH), 1610, 1397, 1110 and 590 cm^{-1} .

Example 3: Synthesis of water-compatible polyhydroxylated fullerene derivatives $\text{C}_{60}(\text{OH})_6$ or $\text{C}_{60}(\text{OH})_8$ (fullereneol-9)

A reaction flask (50 ml) was charged with either hexabromo- C_{60} fullerene (500 mg) [see Birkett, et al., Nature 1992, 357, 479], hexachloro- C_{60} fullerene (500 mg) [see Birkett, et al., J. Chem. Soc., Chem. Commun. 1993, 1230.], or octabromo- C_{60} fullerene (500 mg) [see Birkett, et al., Nature 1992, 357, 479] and DMF (20 ml). The solution mixture was purged with N_2 for 10 min. It was then added tetramethylammonium hydroxide pentahydrate (1.1 equiv. of halogen atom in halogenated fullerene) or other tetraalkylammonium hydroxide (1.1 equiv. of halogen atom in halogenated fullerene, 40% in H_2O) and stirred at 70°C for 2-5 h. At the end of reaction, the resulting solution was concentrated and added methanol (50 ml) to effect precipitation of brown solid. The solid precipitate was isolated by centrifugation. It was then washed twice with methanol (20 ml each time) and dried in vacuum at 40°C to afford brown solid of the corresponding hexahydroxylated, $\text{C}_{60}(\text{OH})_6$, or octahydroxylated, $\text{C}_{60}(\text{OH})_8$, fullerene derivative (350 mg, fullereneol-9). Fullerenols of $\text{C}_{60}(\text{OH})_6$ and $\text{C}_{60}(\text{OH})_8$ have appreciable solubility in DMF.

Example 4: Synthesis of water-soluble polyhydroxylated fullerene derivatives $\text{C}_{60}(\text{OH})_{24}$ (fullereneol-10)

A reaction flask (50 ml) was charged tetracosabromo- C_{60} fullerene (500 mg) [see Tebbe, et al., Science 1992, 256, 822] and DMF (20 ml). The solution mixture was purged with N_2 for 10 min. It was then added tetramethylammonium hydroxide pentahydrate (1.1 equiv. of halogen atom in tetracosabromo- C_{60} fullerene) or other tetraalkylammonium hydroxide (1.1 equiv. of halogen atom in tetracosabromo- C_{60} fullerene, 40% in H_2O) and stirred at 70°C for 2-5 h. At the end of reaction, the resulting solution was concentrated and added methanol (50 ml) to effect precipitation of brown solids. The solid precipitate was isolated by centrifugation. It was then washed twice with methanol (20 ml each time) and dried in vacuum at 40°C to afford brown solid of the corresponding tetracosahydroxylated, $\text{C}_{60}(\text{OH})_{24}$, fullerene derivative (330 mg, fullereneol-10).

Example 5: Synthesis of water-soluble polyhydroxylated fullerene derivatives $\text{C}_{60}(\text{OH})_x$ (fullereneol-11)

A reaction flask (100 ml) was charged with either fullereneol-2 (1.0 g) or fullereneol-9 (1.0 g), DMF (40 ml) and hydrogen peroxide (30% in H_2O , 20 ml). The solution was purged with N_2 for 10 min prior to exposure of UV irradiation (254 nm) for 5-24 h. During the period of irradiation, the color of solution was observed to fade from brown slightly. At the end

of reaction, the resulting mixture was added a mixture of tetrahydrofuran and diethyl ether in a ratio of 1:1 (60 ml) to effect a precipitation of light brown solids. The solid precipitate was isolated by centrifugation. It was then washed twice with a mixture of THF and diethyl ether in a ratio of 2:1 (30 ml each time) and dried in vacuum at 40°C to afford brown solids of water-soluble polyhydroxylated fullerene derivatives $C_{60}(OH)_x$ (835 mg, fullerenol-11 with the number of hydroxy addends of higher than 15 per C_{60} cage). The number of hydroxy addends on the C_{60} cage increased upon the time increase of the sample exposure to UV irradiation. Infrared data of fullerenol-11 are as follow: $IR_{\nu_{\max}}$ (KBr) 3435 (br, OH), 3243 (shoulder), 1650, 1400, 1084 and 577 cm^{-1} .

Example 6: Synthesis of polyhydroxylated fullerene derivatives (fullerenol-5)

A two-necked reaction flask A (50 mL) was equipped with a vertical dropping funnel with a stopcock on one neck and a connecting gas bubbling tube on the other neck. The gas-bubbling tube was attached with a drying tube ($CaCl_2$) and inserted into the second two-necked reaction flask B. The other neck of flask B was attached with a bubbling tube which was extended into a trapping flask containing aqueous sodium hydroxide solution (2 N). To minimize the back-flow of moisture from alkaline solution, a drying tube ($CaCl_2$) was installed in between the flask B and the trapping flask. A steady inert gas (N_2) flow was allowed starting from the top of dropping funnel, through the reaction flasks A and B in sequence, into the alkaline solution in the trapping flask. The dropping funnel and the reaction flask A were charged with conc. HNO_3 (10 mL) and sodium nitrite ($NaNO_2$, 10 g), respectively. In the reaction flask B was placed a solution of C_{60} fullerene (500 mg) in benzen (50 mL, dried over Na). The inert gas bubbling through the C_{60} solution in the flask B was adjusted to a flow rate of 5 mL per min. The fullerene solution was deoxygenated for at least 5 min prior to the reaction. Conc. HNO_3 solution was then allowed to add dropwise into sodium nitrite solids in the flask A. Brown fume was produced immediately upon the contact of conc. HNO_3 with $NaNO_2$. It was carried by the steady flow of N_2 and bubbled through the C_{60} solution in the flask B. Within 15 min of reaction, the purple solution of C_{60} was changed to orange-red progressively. The mixture was stirred at ambient temperature for an additional 2 h to give a dark brown-red solution with suspended solids. At the end of reaction, excessive nitrogen dioxide (NO_2) was removed by N_2 bubbling and destroyed in the trapping solution. Benzene was then evaporated from the product solution at a reduced pressure to give dark brown solids. The solids were suspended in anhydrous *n*-hexane, separated from *n*-hexane solution by centrifugation, and dried in vacuum at 40°C to afford brown solids of polynitro fullerene derivatives, $C_{60}(NO_2)_n$, (650 mg). $IR_{\nu_{\max}}$ (KBr) 1572 [$s, \nu_{as}(N-O)$], 1328 [$s, \nu_s(N-O)$], 1085, 1038, 973, 815 (δ), 760, 733, 696, 545, and 466. Polynitro compound exhibits appreciable solubility in common organic solvents such as THF, DMF, CH_2Cl_2 , CH_3OH , and dimethyl sulfoxide (DMSO).

Polynitro fullerene derivatives, $C_{60}(NO_2)_n$ (500 mg), were added into an aqueous solution of NaOH (3 N, 25 mL). The suspension was stirred and heated at 40°C for 4 h. It was then added slowly into MeOH (80 mL) to effect the precipitation of dark brown solids. The suspended solids were separated from solution by centrifugation, washed 3 times with methanol (15 mL each time) and dried in vacuum at 40°C to afford brown solids of polyhydroxylated fullerene derivatives, $C_{60}(OH)_n$ (fullerenols-5, 430 mg).

One-pot synthesis of fullerenols was performed by the direct hydrolysis of polynitro fullerene derivatives without their isolation from the previous reaction with NO_2 , as follows: At the end of fullerene nitration reaction described above (in the same reaction scale), residual nitrogen dioxide (NO_2) was removed by N_2 bubbling and destroyed in the trapping solution. Benzene was then evaporated from the product solution at a reduced pressure to give solvent-free solids. An aqueous solution of NaOH (3 N, 25 mL) was added. The suspension was stirred and heated at 40°C for 4 h. After cooling the reaction mixture to ambient temperature, it was poured slowly into MeOH (80 mL) to effect the precipitation of dark brown solids of fullerenols. The rest of the workup procedure is identical to that described above for the synthesis of fullerenol-5.

The physical data of compound $C_{60}(OH)_n$ are as follow: $IR_{\nu_{\max}}$ (KBr) 3434 (br, s, OH), 1631, 1387, 1065, and 472; ^{13}C NMR (THF- d_6 , the highest peak of band) δ 147.4, 146.0, 143.2, 72.0-84.0 (very weak). MS (FAB, negative ion, mass of the highest ion peak in the fragmentation group), m/z 576, 600, 624, 648, 672, 696, 720 (rel intensity 100), 736 ($n = 1$), 753 ($n = 2$), 770 ($n = 3$), 787 ($n = 4$), 804 ($n = 5$), 821 ($n = 6$), 838 ($n = 7$), 855 ($n = 8$), 872 ($n = 9$), 889 ($n = 10$), 906 ($n = 11$), 923 ($n = 12$), 940 ($n = 13$), 957 ($n = 14$), 974 ($n = 15$), and 991 ($n = 16$).

Example 7: Synthesis of water-soluble poly(sodium sulfonylbutoxylated) fullerene derivatives $C_{60}(OCH_2CH_2CH_2CH_2SO_3Na)_x$, or poly(sodium sulfonylpropoxylated) fullerene derivatives $C_{60}(OCH_2CH_2CH_2SO_3Na)_x$

A reaction flask (100 ml) was charged with a solution of either fullerenol-2 or fullerenol-9 (500 mg) in DMF (25 ml), which was dried over molecular sieves (4 Å). To this solution was added Na metal (1.2 equiv. of hydroxy group) and the resulting mixture was stirred for 5.0 h to afford a clear brown solution of $C_{60}(ONa)_{12}$ (ave.) for fullerenol-2 and $C_{60}(ONa)_6$ or $C_{60}(ONa)_8$ for fullerenol-9 as versatile reactive intermediates. 1,4-Butane sultone or 1,3-propane sultone (1.2 equiv. of hydroxy group) was then added and the solution was stirred at ambient temperature for 4 h. At the end of reaction, it

was added methanol (80 ml) to cause the precipitation of brown solids. The solid precipitate was isolated by centrifugation. It was then washed twice with methanol (30 ml each time) and dried in vacuum at 40°C to afford brown solids of water-soluble poly(sodium sulfonylbutoxylated), $C_{60}(OCH_2CH_2CH_2CH_2SO_3Na)_x$, or poly(sodium sulfonylpropoxylated), $C_{60}(OCH_2CH_2CH_2SO_3Na)_x$, fullerene derivatives corresponding to 1,4-butane sultone or 1,3-propane sultone used, respectively. In the reactions where fullerenol-9 and 1.2 equiv. of sultone reagent per hydroxy group were used as the reagents, the exact chemical composition of $C_{60}(OCH_2CH_2CH_2CH_2SO_3Na)_6$ or $C_{60}(OCH_2CH_2CH_2CH_2SO_3Na)_8$ was obtained.

Example 8: Synthesis of poly(organoxylated) fullerene derivatives $C_{60}(-O-B-C-D)_x$

A reaction flask (100 ml) was charged with a solution of either fullerenol-2 or fullerenol-9 (500 mg) in DMF (25 ml), which was dried over molecular sieves (4 Å). To this solution was added Na metal (1.2 equiv. of hydroxy group) and the resulting mixture was stirred for 5.0 h to afford a clear brown solution of $C_{60}(-ONa)_{12}$ (ave.) for fullerenol-2 and $C_{60}(-ONa)_6$ or $C_{60}(-ONa)_8$ for fullerenol-9 as versatile reactive intermediates. Reagent with a reactive leaving-group such as Br-B-C-D, $CH_3SO_2O-B-C-D$, or $CF_3SO_2O-B-C-D$ (1.2 equiv. of hydroxy group) was then added and the solution was stirred at ambient temperature to 70°C for 4 h. At the end of reaction, diethyl ether (80 ml) was added to cause the precipitation of brown solids. The solid precipitate was isolated by centrifugation, and then washed twice with diethyl ether (30 ml each time) and dried in vacuum at 40°C to afford brown solids of the corresponding poly(organoxylated), $C_{60}(-O-B-C-D)_x$, fullerene derivatives. In reactions where fullerenol-9 was used as a reagent, the exact chemical composition of $C_{60}(-O-B-C-D)_6$ or $C_{60}(-O-B-C-D)_8$ was obtained. With the amino protecting group $-N(COCH_2)_2$, the hydroxy protecting group $-O-Si(CH_3)_3$, and the thiol protecting group $-S-CH_2-Ar$, a deprotection reaction can be carried out with $C_{60}(-O-B-C-D)_x$ to give the corresponding $-NH_2$, $-OH$, and $-SH$ end groups.

In this experiment, B and C, in combination, form a C_6 alkyl group, and D is OH (protected by $-N(COCH_2)_2$). However, B, C and D (properly protected, if necessary) can be any of the respective moieties assigned to them in the "Summary of the Invention" section with the exceptions of polyanhydride and polycarbonate.

Example 9: Synthesis of water-soluble poly(sodium sulfonylbutoxylated) fullerene derivative

$C_{60}(CH_2CH_2CH_2CH_2SO_3Na)_x$ or poly(sodium sulfonylpropylated) fullerene derivative $C_{60}(CH_2CH_2CH_2SO_3Na)_x$

A round-bottom reaction flask A (100 ml) equipped with a magnetic stirrer was fitted with a septum and purged with N_2 . It was charged with fullerene (500 mg), pure C_{60} or fullerene mixtures, toluene (40 ml) and 1,4-butane sultone or 1,3-propane sultone (5-20 equiv. of fullerene). The solution was dried over molecular sieves (4 Å) prior to use. In a separated flask B, naphthalene (5-20 equiv. of fullerene) dissolved in dimethoxyethane (DME, 10 ml, dried over molecular sieves 4 Å prior to use) was allowed to react with sodium (5-20 equiv. of fullerene), forming a greenish complex solution of sodium naphthalide. This sodium naphthalide solution was then added into the reaction flask A via the syringe technique. The mixture was stirred at ambient temperature for 4 h under N_2 . At the end of reaction, it was added H_2O (2 ml) to quench all reactive intermediates and the resulting solution was added into methanol (60 ml) to effect precipitation of brown solids. The solid precipitate was isolated by centrifugation. It was then washed twice with methanol (20 ml each time) and dried in vacuum at 40°C to afford brown solids of water-soluble poly(sodium sulfonylbutoxylated), $C_{60}(CH_2CH_2CH_2CH_2SO_3Na)_x$, or poly(sodium sulfonylpropylated), $C_{60}(CH_2CH_2CH_2SO_3Na)_x$, fullerene derivatives corresponding to 1,4-butane sultone or 1,3-propane sultone used, respectively. The value of x varies with the amount of sodium naphthalide used in the reaction. Infrared data of poly(sodium sulfonylalkylated) fullerene derivatives are as follow: IR_{max} (KBr) 1642, 1570, 1384, 1192, 1038, 797, 750, 603 and 534 cm^{-1} .

Example 10: Synthesis of poly(functional alkylated) fullerene derivatives $C_{60}(-CH_2-B-C-D)_x$

A round-bottom reaction flask A (100 ml) equipped with a magnetic stirrer was fitted with a septum and purged with N_2 . It was charged with fullerene (500 mg), pure C_{60} or fullerene mixtures, toluene (40 ml) and $CH_3SO_2O-CH_2-B-C-D$ or $CF_3SO_2O-CH_2-B-C-D$ (5-20 equiv. of fullerene). The solution was dried over molecular sieves (4 Å) prior to use. In a separated flask B, naphthalene (5-20 equiv. of fullerene) dissolved in DME (10 ml) and dried over molecular sieves (4 Å) prior to use was allowed to react with sodium (5-20 equiv. of fullerene), forming a greenish complex solution of sodium naphthalide. This sodium naphthalide solution was then added into the reaction flask A via the syringe technique. The mixture was stirred at ambient temperature for 4 h under N_2 . At the end of reaction, it was added H_2O (2 ml) to quench all reactive intermediates and the resulting solution was added into methanol (60 ml) to effect precipitation of brown solids. The solid precipitate was isolated by centrifugation. It was then washed twice with methanol (20 ml each time) and dried in vacuum at 40°C to afford brown solids of poly(functional alkylated) fullerene derivatives $C_{60}(-CH_2-B-C-D)_x$. The value of x varies with the amount of sodium naphthalide used in the reaction. With the amino protecting group $-N(COCH_2)_2$, the hydroxy protecting group $-O-Si(CH_3)_3$, and the thiol protecting group $-S-CH_2-Ar$, a deprotection reaction can be carried out with $C_{60}(-O-B-C-D)_x$ to give the corresponding $-NH_2$, $-OH$, and $-SH$ end groups.

In this experiment, B and C, in combination, form a C_6 alkyl group, and D is OH (protected by $-N(COCH_2)_2$). However, B can be any of the following: $-R-O-[Si(CH_3)_2-O]_{1-100}$, C_{1-2000} alkyl, C_{6-40} aryl, C_{7-60} alkylaryl, C_{7-60} arylalkyl, $(C_{2-30}$ alkyl ether) $_{1-100}$, $(C_{6-40}$ aryl ether) $_{1-100}$, $(C_{7-60}$ alkylaryl ether) $_{1-100}$, $(C_{7-60}$ arylalkyl ether) $_{1-100}$, $(C_{2-30}$ alkyl thioether) $_{1-100}$, $(C_{6-40}$ aryl thioether) $_{1-100}$, $(C_{7-60}$ alkylaryl thioether) $_{1-100}$, $(C_{7-60}$ arylalkyl thioether) $_{1-100}$. C can be any of the following: $-R-$, $-R-Ar-$, $-Ar-R-$, or $-Ar-$. D (properly protected, if necessary) can be any of the following: $-H$, $-O-Si(CH_3)_3$, $-S-CH_2-Ar$, $-SO_3^-$, $-OSO_3^-$, $-CO_2^-$, $-PO_3^-$, $-O-PO(O^-)-O-PO_3^{2-}$, $-O-PO_3^{2-}$, $-O-PO(O^-)-O-PO(O^-)-O-PO_3^{2-}$, $-N(COCH_2)_2$, or $-NR_1R_2$, each of R , R_1 , and R_2 being independently C_{1-20} alkyl and Ar being aryl.

Example 11: Synthesis of hexamino fullerene derivatives $C_{60}(-NH_2)_6$, octamino fullerene derivatives $C_{60}(-NH_2)_8$, and tetracosamino fullerene derivatives $C_{60}(-NH_2)_{24}$ (fullerenamines)

A round-bottom reaction flask (100 ml) equipped with a magnetic stirrer was fitted with a septum and a cool-trap condenser. It was charged with either hexabromo- C_{60} fullerene (500 mg; see Birkett, et al., Nature 1992, 357, 479), hexachloro- C_{60} fullerene (500 mg; see Birkett, et al., Chem. Soc., Chem. Commun. 1993, 1230), octabromo- C_{60} fullerene (500 mg; see Birkett, et al., Nature 1992, 357, 479) or tetracosabromo- C_{60} fullerene (500 mg; see Tebbe, et al., Science 1992, 256, 822), DMF (20 ml) and 4-dimethylamino-pyridine or 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU, 450 mg). The solution was slowly bubbled with NH_3 gas (20 ml per min) at $60^\circ C$ for 7 h with the dry-ice/acetone filling in the cool-trap. At the end of reaction, the resulting solution was added methanol (60 ml) to effect precipitation of brown solids. The solid precipitate was isolated by centrifugation. It was then washed twice with methanol (20 ml each time) and dried in vacuum at $40^\circ C$ to afford brown solid of the corresponding hexamino fullerene derivative $C_{60}(NH_2)_6$, octamino fullerene derivative $C_{60}(NH_2)_8$, or tetracosamino fullerene derivative $C_{60}(NH_2)_{24}$. Fullerenamines of $C_{60}(NH_2)_6$ and $C_{60}(NH_2)_8$ have appreciable solubility in DMF and $C_{60}(NH_2)_{24}$ is soluble in water.

Example 12: Synthesis of hexamino fullerene derivatives $C_{60}(-NH_2)_6$, octamino fullerene derivatives $C_{60}(-NH_2)_8$, and tetracosamino fullerene derivatives $C_{60}(-NH_2)_{24}$ (fullerenamine)

A round-bottom reaction flask A (100 ml) equipped with a magnetic stirrer was fitted with a septum and purged with N_2 . It was charged with either hexabromo- C_{60} fullerene (500 mg; see Birkett, et al., Nature 1992, 357, 479), hexachloro- C_{60} fullerene (500 mg; see Birkett, et al., Chem. Soc., Chem. Commun. 1993, 1230), octabromo- C_{60} fullerene (500 mg; see Birkett, et al., Nature 1992, 357, 479) or tetracosabromo- C_{60} fullerene (500 mg; see Tebbe, et al., Science 1992, 256, 822) and DMF (20 ml). In a separated reaction flask B, benzamide (1.1 equiv. of halogen group in halogenated fullerene) was allowed to react with sodium hydride (1.1 equiv. of benzamide) in THF (20 ml, distilled over Na) at ambient temperature to afford immediately the corresponding solution of sodium benzamide ($C_6H_5CONHNa$). The solution was added portionwise into the reaction flask A at $0^\circ C$ and the mixture was stirred further at that temperature for an additional 3 h. At the end of reaction, all solvents were removed from the resulting solution in vacuum to give brown solids. These solids were transferred into an aqueous solution of NaOH (15 ml, 3N) and the mixture was stirred and heated at $90^\circ C$ for 16 h. It was cooled to ambient temperature and added methanol (60 ml) to cause precipitation of dark brown solids. The solid precipitate was isolated by centrifugation. It was then washed twice with methanol (20 ml each time) and dried in vacuum at $40^\circ C$ to afford brown solid of the corresponding hexamino fullerene derivative $C_{60}(NH_2)_6$, octamino fullerene derivative $C_{60}(NH_2)_8$, or tetracosamino fullerene derivative $C_{60}(NH_2)_{24}$.

Example 13: Synthesis of functionalized hexaorgano fullerene derivatives $C_{60}(-A-B-C-D)_6$, octaorgano fullerene derivatives $C_{60}(-A-B-C-D)_8$, and tetracosaoorgano fullerene derivatives $C_{60}(-A-B-C-D)_{24}$

A round-bottom reaction flask (100 ml) equipped with a magnetic stirrer was fitted with a septum and purged with N_2 . It was charged with either hexabromo- C_{60} fullerene (500 mg; see Birkett, et al., Nature 1992, 357, 479), hexachloro- C_{60} fullerene (500 mg; see Birkett, et al., Chem. Soc., Chem. Commun. 1993, 1230), octabromo- C_{60} fullerene (500 mg; see Birkett, et al., Nature 1992, 357, 479) or tetracosabromo- C_{60} fullerene (500 mg; see Tebbe, et al., Science 1992, 256, 822), THF (20 ml, distilled over Na) and 4-dimethyl-aminopyridine or DBU (450 mg). It was added either $HO-B-C-D$, $H_2N-B-C-D$, or $HS-B-C-D$ (1.3 equiv. of halogen group in halogenated fullerene) and the mixture was stirred and heated at $70^\circ C$ for 16 h. At the end of reaction, THF was evaporated from the resulting solution to afford pale brown to brown solids. The solid was added into water (30 ml) with stirring to give fine suspension of products. The solid precipitate was isolated by centrifugation. It was then washed twice with water (20 ml each time), twice with diethyl ether (20 ml each time), and dried in vacuum at $40^\circ C$ to afford pale brown to brown solids of the corresponding functionalized hexaorgano fullerene derivatives $C_{60}(-A-B-C-D)_6$, octaorgano fullerene derivatives $C_{60}(-A-B-C-D)_8$, and tetracosaoorgano fullerene derivatives $C_{60}(-A-B-C-D)_{24}$.

In this experiment A is $-O-$, B and C in combination form C_6 alkyl, and D is $-OH$ and $-O-Si(CH_3)_3$. However, B, C and D (properly protected, if necessary) can be any of the respective moieties assigned to them in the "Summary of the Invention" section.

Example 14: Synthesis of Polyamino Fullerene Derivatives, $C_{60}(-NH_2)_n$ (fullerenamine)

A two-necked reaction flask A (50 mL) was equipped with a vertical dropping funnel with a stopcock on one neck and a connecting gas bubbling tube on the other neck. The gas-bubbling tube was attached with a drying tube ($CaCl_2$) and inserted into the second two-necked reaction flask B. The other neck of flask B was attached with a bubbling tube which was extended into a trapping flask containing aqueous sodium hydroxide solution (2 N). To minimize the back-flow of moisture from alkaline solution, a drying tube ($CaCl_2$) was installed in between the flask B and the trapping flask. A steady inert gas (N_2) flow was allowed starting from the top of dropping funnel, through the reaction flasks A and B in sequence, into the alkaline solution in the trapping flask. The dropping funnel and the reaction flask A were charged with conc. HNO_3 (10 mL) and copper powder (10 g) or sodium nitrite ($NaNO_2$, 10 g), respectively. In the reaction flask B was placed a solution of C_{60} fullerene (500 mg) in benzene (50 mL, dried over Na). The inert gas bubbling through the C_{60} solution in the flask B was adjusted to a flow rate of 5 mL per min. The fullerene solution was deoxygenated for at least 5 min prior to the reaction. Conc. HNO_3 solution was then allowed to add dropwise into sodium nitrite solids in the flask A. Brown fume was produced immediately upon the contact of conc. HNO_3 with $NaNO_2$. It was carried by the steady flow of N_2 and bubbled through the C_{60} solution in the flask B. Within 15 min of reaction, the purple solution of C_{60} was changed to orange-red progressively. The mixture was stirred at ambient temperature for an additional 2 h to give a dark brown-red solution with suspended solids. At the end of reaction, excessive nitrogen dioxide (NO_2) was removed by N_2 bubbling and destroyed in the trapping solution. Benzene was then evaporated from the product solution at a reduced pressure to give dark brown solids. The solids were suspended in anhydrous *n*-hexane, separated from *n*-hexane solution by centrifugation and dried in vacuum at $40^\circ C$ to afford brown solids of polynitro fullerene derivatives, $C_{60}(NO_2)_n$ ($n = 12$ on average) (650 mg). $IR_{\nu_{max}}$ (KBr) 1572 [$\nu_{as}(N-O)$], 1328 [$\nu_s(N-O)$], 1085, 1038, 973, 815 (δ), 760, 733, 696, 545, and 466. Polynitro compound exhibits appreciable solubility in common organic solvents such as THF, DMF, CH_2Cl_2 , CH_3OH and DMSO.

A round-bottom reaction flask (100 ml) equipped with a magnetic stirrer was fitted with a septum and a cool-trap condenser. It was charged with polynitro fullerene derivatives, $C_{60}(NO_2)_n$, (500 mg), DMF (20 ml) and 4-dimethylaminopyridine or DBU (450 mg). The solution was slowly bubbled with NH_3 gas (20 ml per min) at $60^\circ C$ for 7 h with the dry-ice/acetone filling in the cool-trap. At the end of reaction, the resulting solution was added methanol (60 ml) to effect precipitation of brown solids. The solid precipitate was isolated by centrifugation. It was then washed twice with methanol (20 ml each time) and dried in vacuum at $40^\circ C$ to afford brown solid of the corresponding polyamino fullerene derivative $C_{60}(NH_2)_n$ ($n = 16$ on average). The increase of n is due to the further slow nucleophilic addition of NH_3 on polyaminated fullerenes under basic conditions. Therefore, the increase is time and pH dependent.

Example 15: Synthesis of polyamino fullerene derivatives, $C_{60}(-NH_2)_n$ (fullerenamine)

A round-bottom reaction flask (100 ml) equipped with a magnetic stirrer was fitted with a septum and a cool-trap condenser. It was charged with polynitro fullerene derivatives, $C_{60}(NO_2)_n$, synthetically described in Example 14 (500 mg) and DMF (20 ml). The solution was added $NaNH_2$ (400 mg) and stirred at $60^\circ C$ for 7 h. At the end of reaction, the resulting solution was added methanol (60 ml) to effect precipitation of brown solids. The solid precipitate was isolated by centrifugation. It was then washed twice with methanol (20 ml each time) and dried in vacuum at $40^\circ C$ to afford brown solid of the corresponding polyamino fullerene derivative $C_{60}(-NH_2)_n$.

Example 16: Synthesis of polyamino fullerene derivatives, $C_{60}(-NH_2)_n$ (fullerenamine)

A round-bottom reaction flask A (100 ml) equipped with a magnetic stirrer was fitted with a septum and purged with N_2 . It was charged with polynitro fullerene derivatives, $C_{60}(NO_2)_n$, synthetically described in Example 14 (500 mg) and DMF (20 ml). In a separated reaction flask B, benzamide (1.1 equiv. of halogen group in halogenated fullerene) was allowed to react with sodium hydride (1.1 equiv. of benzamide) in THF (20 ml, distilled over Na) at ambient temperature to afford immediately the corresponding solution of sodium benzamide ($C_6H_5CONHNa$). The solution was added portionwise into the reaction flask A at $0^\circ C$ and the mixture was stirred further at that temperature for an additional 3 h. At the end of reaction, all solvents were removed from the resulting solution in vacuum to give brown solids. These solids were transferred into an aqueous solution of NaOH (15 ml, 3 N) and the mixture was stirred and heated at $90^\circ C$ for 16 h. It was cooled to ambient temperature and added methanol (60 ml) to cause precipitation of dark brown solids. The solid precipitate was isolated by centrifugation. It was then washed twice with methanol (20 ml each time) and dried in vacuum at $40^\circ C$ to afford brown solids of the corresponding polyamino fullerene derivative, $C_{60}(NH_2)_n$ where n is about

Example 18 Synthesis of polyamino fullerene derived compounds, $C_{60}(-NH-CO-NH-B-C-D)_x$

30 **Example 19 Synthesis of polyamino fullerene derived compounds, $C_{60}(-NH-CO-B-C-D)_x$**

Example 20: Detection of superoxide radicals in whole blood

Biological evaluations of water-soluble fulleranol-1 as a free-radical scavenger were performed on heparinized whole blood samples from different patients (both males and females of different ages) with acute pancreatitis, gastric cancer, breast cancer, or gastric ulcer. The whole blood samples used in the study were acquired from patients in the early morning after 12 hrs of fasting. The heparinized blood (treated by mucopolysaccharide acid) was wrapped immediately with aluminum foil to minimize possible light exposure and kept at 5°C prior to the testing within approximately 2 h. In each measurement, heparinized blood (0.2 ml) placed inside a stainless cell (5 cm in diameter) in an absolutely dark chamber of a chemiluminescence analyzing system was charged with phosphate-buffered solution (PBS; 0.1 ml, pH 7.4). Photon emission from the whole blood was counted at an interval of 10 sec at 37°C under atmospheric condi-

0.01 mM) in PBS buffer solution was injected into the cell and the chemiluminescence emitted from the blood sample was continuously measured for an additional period of 400 sec. In the study, the total count of chemiluminescence was calculated by integrating the area under the chemiluminescence-vs-time curve and then subtracting it from the background level. Note that in control experiments, superoxide dismutase was found to decrease chemiluminescence intensity, indicating the existence of superoxide radicals in the blood samples.

Referring to Fig. 1, a whole blood sample from a male patient with acute pancreatitis (age 60) showed the chemiluminescence intensity level of 2888 counts/10 sec after the addition of lucigenin. When a whole blood sample from the same patient was pre-treated with fullereneol-1 at a concentration of 60 µg/ml, a much lower chemiluminescence intensity level, i.e., 397 counts/10 sec, was observed, indicating that fullereneol-1 has a free-radical scavenging efficiency of 86.3%. More results from other patients with acute pancreatitis, breast cancer, and gastric cancer are listed in the table below:

Disease	Sex	Age	F*	Counts*	Decrease (%)
Acute pancreatitis	F	60	0	648.2	52.7
			60	306.5	
Acute pancreatitis	M	60	0	2887.9	86.3
			60	397.0	
Acute pancreatitis	F	42	0	4945.9	75.6
			80	1206.7	
Acute pancreatitis	F	42	0	7157.8	82.2
			60	1275.4	
			80	1335.0	
Acute pancreatitis	M	60	0	5802.3	74.0
			60	1508.1	
Acute pancreatitis	M	78	0	2167.3	47.4
			60	1139.3	
			80	618.7	
Breast cancer	F	38	0	1537.7	61.2
			60	596.6	
Gastric ulcer	M	67	0	741.7	22.2
			60	576.9	
Gastric cancer	M	69	0	2601.2	77.9
			60	575.5	
Gastric cancer	F	72	0	1679.7	43.5
			10	948.4	
Gastric cancer	F	56	0	1237.0	85.3
			60	182.4	

* Fullereneol-1 in µg/ml
+ Counts in 10 seconds

Example 21: Measurement of radical scavenging activity in vascular rings

The measurement of superoxide production in vascular rings was performed according to a method modified from that reported by Heim, et al., J. Pharmacol. Exp. Ther. 1991, 256, 537. More specifically, vascular rings were incubated

at 37°C under 5% CO₂ in O₂. The diabetogenic drug alloxan, a stimulant for the production of O₂^{•-}, was introduced into the incubation medium followed immediately by the addition of Cytochrome C (37.5 M), the reduction of which is known to be induced by superoxide radical. At the end of incubation period, N-ethylmaleimide (3 mM) was added to prevent further reduction of cytochrome C. These steps were repeated as a sequential test with intermediate rinsings with a buffer solution. To ensure that O₂^{•-} was responsible for the reduction of cytochrome C, some samples were incubated in the presence of superoxide dismutase. As a result, a complete inhibition of cytochrome C reduction upon addition of superoxide dismutase was observed, indicating a correlation between O₂^{•-} and cytochrome C. The quantity of reduced cytochrome containing a low oxidation state of iron (Fe⁺²) was detected and calculated by the extinction coefficient of its specific optical absorption at $\lambda = 550$ nm. After the test, each vascular ring was opened and the area of endothelial surface was measured. Thus, the quantity of O₂^{•-} produced in the test can be expressed in nmol per cm² per min.

When evaluating the free radical-scavenging efficiency of fullereneol-1 or fullereneol-2, the vascular ring was allowed to contact with the fullereneol for at least 10 min prior to the addition of alloxan. The alloxan-stimulated production of O₂^{•-} from intact vascular rings follows a dose-dependent relationship. It was found that a suitable concentration of alloxan (10 mM) significantly increased the production of O₂^{•-} to a level of 326.8±36.6 nmol/cm²/min (n = 5). The production of O₂^{•-} was then gradually depressed by the pre-treatment of vascular rings with the fullereneol at a concentration of 10⁻⁶, 10⁻⁵ and 10⁻⁴ M. Such results indicate that the fullereneol acted as a superoxide radical scavenger in vascular rings.

Example 22: Antiproliferative activities

The antiproliferative activities of both fullereneol-1 and fullereneol-2 were measured as their ability to inhibit the proliferation of cultured rabbit aortic smooth muscle cells induced by the fetal calf serum. See Huang, Et al., Eur. J. Pharmacol. 1992, 221, 381. More specifically, the intima and inner two-thirds of the cell-containing media were removed from the isolated rabbit aorta in strips of 1 mm in width. The strips were further cut into square pieces and placed in a dry petri dish. The dish was then filled with the DMEM medium supplemented with 10% fetal calf serum. When the cells approached confluence, the aorta pieces were removed. Cells between passages 3 and 8 were used, and their viability was determined by the trypan blue dye exclusion method. The proliferative response of vascular smooth muscle cells was determined based on the uptake of tritiated thymidine for DNA synthesis. Prior to all experiments, confluent smooth muscle cells (2.5 x 10⁴ cells/well) were rendered quiescent by culturing for 48 h in 0.5% fetal calf serum. The medium was then charged with stimulator, i.e., 5% fetal calf serum, and the fullereneol. The resulting mixture was kept for 24 h before the subsequent addition of [³H]thymidine (0.2 Ci/well). After an additional twenty-four hr of culturing, the cells were harvested and the incorporated [³H]thymidine was counted by a liquid scintillation counter. Each experiment was performed in triplicate.

The inhibitory activities of fullereneol-1 and fullereneol-2 were expressed as percentages of the untreated control value obtained upon addition of stimulator under similar conditions in the absence of fullerenols. The concentration evoking 50% of the maximal inhibition (IC₅₀) was calculated accordingly for each experiment. The control value for the incorporation of [³H]thymidine in proliferative cultures of rabbit vascular smooth muscle cells, induced by 5% fetal calf serum, was found to be 12527±2011 cpm/well. Exposure of smooth muscle cells to fullerenols, in a dose range of 10⁻⁷ to 10⁻⁴ M, inhibited significantly the incorporation of [³H]thymidine. As shown in Fig. 2, a sharp decrease of proliferative response was observed as the dose concentrations increased. The IC₅₀ values (n = 7) were determined to be 0.30±0.07 μ M for fullereneol-1 and 2.2±0.5 μ M for fullereneol-2. The maximal inhibitory activities of water-soluble fullerenols at a dose level of 10⁻⁴ M were found to be 98.0±1.7% for fullereneol-1 and 87.0±9.8% for fullereneol-2. Comparison of these data with the inhibitory activities of ascorbic acid (vitamin C) shows that it requires more than 130 times as much ascorbic acid as fullereneol-1 to achieve 50% inhibition of the proliferative activities. These results demonstrated, for the first time, that water-soluble fullerenols exhibited the antiproliferative effects on rabbit vascular smooth muscle cells.

Much higher antiproliferative activities of fullereneol-1 and fullereneol-2, as compared with ascorbic acid, were also observed with human T-lymphoid leukemia CEM cells (obtained from the American Type Culture Collection, Rockville, MD). More specifically, IC₅₀ values (n = 5) of fullereneol-1 and fullereneol-2 were determined to be 3.5±0.6 μ M and 4.3±0.8 μ M. Indeed, the IC₅₀ value of fullereneol-1 is 60 times that of ascorbic acid. The maximal inhibitory activities of fullereneol-1 and fullereneol-2 were found to be 86.0±3.1% and 87.0±3.0%, respectively.

Other Embodiments

From the above description, one skilled in the art can easily ascertain the essential characteristics of the present invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions. For example, counter ionic salts, if any, of the fullerene derivatives described above and their use are within the scope of this invention. As another example, while only fullerene derivatives containing poly(simple ether) substituents are described herein, fullerene derivatives containing poly(mixed

ether) substituents, either by themselves or as components of compositions, are also covered by this invention under the doctrine of equivalents. Thus, other embodiments are also within the claims.

Claims

1. A compound of formula I



wherein

F is a fullerene core:

each X is independently $-\text{CO}_2^-$, $-\text{SO}_3^-$, $-\text{OH}$, $-\text{SH}$, $-\text{PO}_3^-$, $-\text{O-PO}_3^{2-}$, $-\text{O-PO}(\text{O}^-)\text{-O-PO}_3^{2-}$, $-\text{O-PO}(\text{O}^-)\text{-O-PO}(\text{O}^-)\text{-O-PO}_3^{2-}$, $-\text{O-PO}(\text{O}^-)\text{-O-CH}_2\text{-CH}_2\text{-NH}_3^+$, $-\text{NH}_2$, NH_3^+ , $-\text{N+H}_2\text{R}_a$, $\text{N+HR}_a\text{R}_b$ or $-\text{N+R}_a\text{R}_b\text{R}_c$;

each Y is -A-B-, in which A is independently -CH₂-, -O-, -S-, -NH-CO-NH-, or -NH-CO-, and B is independently -R₂-O-[Si(CH₃)₂-O]₁₋₁₀₀, C₁₋₂₀₀₀ alkyl, C₆₋₄₀ aryl, C₇₋₆₀ alkylaryl, C₇₋₆₀ arylalkyl, (C₁₋₃₀ alkyl ether)₁₋₁₀₀, (C₆₋₄₀ aryl ether)₁₋₁₀₀, (C₇₋₆₀ alkylaryl ether)₁₋₁₀₀, (C₇₋₆₀ arylalkyl ether)₁₋₁₀₀, (C₁₋₃₀ alkyl thioether)₁₋₁₀₀, (C₆₋₄₀ aryl thioether)₁₋₁₀₀, (C₇₋₆₀ alkylaryl thioether)₁₋₁₀₀, (C₇₋₆₀ arylalkyl thioether)₁₋₁₀₀, (C₂₋₅₀ alkyl ester)₁₋₁₀₀, (C₇₋₆₀ aryl ester)₁₋₁₀₀, (C₈₋₇₀ alkylaryl ester)₁₋₁₀₀, (C₈₋₇₀ arylalkyl ester)₁₋₁₀₀, -R-CO-O-(C₁₋₃₀ alkyl ether)₁₋₁₀₀, -R-CO-O-(C₆₋₄₀ aryl ether)₁₋₁₀₀, -R-CO-O-(C₇₋₆₀ alkylaryl ether)₁₋₁₀₀, -R-CO-O-(C₇₋₆₀ arylalkyl ether)₁₋₁₀₀, (C₄₋₅₀ alkyl urethane)₁₋₁₀₀, (C₁₄₋₆₀ aryl urethane)₁₋₁₀₀, (C₁₀₋₈₀ alkylaryl urethane)₁₋₁₀₀, (C₁₀₋₈₀ arylalkyl urethane)₁₋₁₀₀, (C₅₋₅₀ alkyl urea)₁₋₁₀₀, (C₁₄₋₆₀ aryl urea)₁₋₁₀₀, (C₁₀₋₈₀ alkylaryl urea)₁₋₁₀₀, (C₁₀₋₈₀ arylalkyl urea)₁₋₁₀₀, (C₂₋₅₀ alkyl amide)₁₋₁₀₀, (C₇₋₆₀ aryl amide)₁₋₁₀₀, (C₈₋₇₀ alkylaryl amide)₁₋₁₀₀, (C₈₋₇₀ arylalkyl amide)₁₋₁₀₀, (C₃₋₃₀ alkyl anhydride)₁₋₁₀₀, (C₈₋₅₀ aryl anhydride)₁₋₁₀₀, (C₉₋₆₀ alkylaryl anhydride)₁₋₁₀₀, (C₉₋₆₀ arylalkyl anhydride)₁₋₁₀₀, (C₂₋₃₀ alkyl carbonate)₁₋₁₀₀, (C₇₋₅₀ aryl carbonate)₁₋₁₀₀, (C₈₋₆₀ alkylaryl carbonate)₁₋₁₀₀, (C₈₋₆₀ arylalkyl carbonate)₁₋₁₀₀, -R₁-O-CO-NH-(R₂ or Ar-R₂-Ar)-NH-CO-O-(C₁₋₃₀ alkyl ether, C₆₋₄₀ aryl ether, C₇₋₆₀ alkylaryl ether, or C₇₋₆₀ arylalkyl ether)₁₋₁₀₀, -R₁-O-CO-NH-(R₂ or Ar-R₂-Ar)-NH-CO-O-(C₂₋₅₀ alkyl ester, C₇₋₆₀ aryl ester, C₈₋₇₀ alkylaryl ester, or C₈₋₇₀ arylalkyl ester)₁₋₁₀₀, -R₁-O-CO-NH-(R₂ or Ar-R₂-Ar)-NH-CO-O-(C₁₋₃₀ alkyl ether, C₆₋₄₀ aryl ether, C₇₋₆₀ alkylaryl ether, or C₇₋₆₀ arylalkyl ether)₁₋₁₀₀-CO-NH-(R₂ or Ar-R₂-Ar)-NH-CO-O-, -R₁-O-CO-NH-(R₂ or Ar-R₂-Ar)-NH-CO-O-(C₂₋₅₀ alkyl ester, C₇₋₆₀ aryl ester, C₈₋₇₀ alkylaryl ester, or C₈₋₇₀ arylalkyl ester)₁₋₁₀₀-R₃-O-CO-NH-(R₂ or Ar-R₂-Ar)-NH-CO-O-, -R₁-NH-CO-NH-(R₂ or Ar-R₂-Ar)-NH-CO-O-(C₁₋₃₀ alkyl ether, C₆₋₄₀ aryl ether, C₇₋₆₀ alkylaryl ether, or C₇₋₆₀ arylalkyl ether)₁₋₁₀₀, -R₁-NH-CO-NH-(R₂ or Ar-R₂-Ar)-NH-CO-O-(C₂₋₅₀ alkyl ester, C₇₋₆₀ aryl ester, C₈₋₇₀ alkylaryl ester, or C₈₋₇₀ arylalkyl ester)₁₋₁₀₀, -R₁-NH-CO-NH-(R₂ or Ar-R₂-Ar)-NH-CO-O-(C₁₋₃₀ alkyl ether, C₆₋₄₀ aryl ether, C₇₋₆₀ alkylaryl ether, or C₇₋₆₀ arylalkyl ether)₁₋₁₀₀-CO-NH-(R₂ or Ar-R₂-Ar)-NH-CO-O-, -R₁-NH-CO-NH-(R₂ or Ar-R₂-Ar)-NH-CO-O-(C₂₋₅₀ alkyl ester, C₇₋₆₀ aryl ester, C₈₋₇₀ alkylaryl ester, or C₈₋₇₀ arylalkyl ester)₁₋₁₀₀-R₃-O-CO-NH-(R₂ or Ar-R₂-Ar)-NH-CO-O-, -R₁-O-CO-NH-(R₂ or Ar-R₂-Ar)-NH-CO-NH-(C₂₋₅₀ alkyl amide, C₇₋₆₀ aryl amide, C₇₋₇₀ alkylaryl amide, or C₇₋₇₀ arylalkyl amide)₁₋₁₀₀, or -R₁-NH-CO-NH-(R₂ or Ar-R₂-Ar)-NH-CO-NH-(C₂₋₅₀ alkyl amide, C₇₋₆₀ aryl amide, C₇₋₇₀ alkylaryl amide, or C₇₋₇₀ arylalkyl amide)₁₋₁₀₀;

each Z is -C-D, wherein C is independently -R-, -R-Ar-, -Ar-, or -Ar-R-; and D is independently -OH, -SH, -SO₃⁻, -OSO₃⁻, -CO₂⁻, -PO₃⁻, -O-PO₃²⁻, -O-PO(O⁻)-O-PO₃²⁻, -O-PO(O⁻)-O-PO(O⁻)-O-PO₃²⁻, -O-PO(O⁻)-O-CH₂-CH₂-NH₃⁺, -NH₂, NH₃⁺, -N+H₂R_a, N⁺HR_aR_b or -N⁺R_aR_bR_c; and

m is 0-30, n is 0-30 and the sum of m and n is 2-30 with the proviso that where X is -OH, -NH₂, NH₃⁺, -N⁺H₂R_a, -N⁺H₂R_aR_b or -N⁺R_aR_bR_c then n is at least 1;
in which each of R, R₁, R₂, R₃, R_a, R_b, R_c, R_d, R_e, R_f and R_g is independently C₁₋₂₀ alkyl, and Ar is independently C₆₋₄₀ aryl, or a salt thereof.

2. A compound of formula I as claimed in claim 1 wherein

each X is independently $-\text{CO}_2^-$, $-\text{SO}_3^-$, $-\text{SH}$, $-\text{PO}_3^-$, $-\text{O}-\text{PO}_3^{2-}$, $-\text{O}-\text{PO}(\text{O}^-)-\text{O}-\text{PO}_3^{2-}$, $-\text{O}-\text{PO}(\text{O}^-)-\text{O}-\text{PO}(\text{O}^-)-\text{O}-\text{PO}_3^{2-}$, $-\text{O}-\text{PO}(\text{O}^-)-\text{O}-\text{CH}_2-\text{CH}_2-\text{NH}_3^+$ or a salt thereof.

3. A compound of formula I as claimed in either one of claims 1 and 2 wherein

each B is independently -R₄-O-[Si(CH₃)₂-O]₁₋₁₀₀, C₁₋₂₀₀₀ alkyl, C₆₋₄₀ aryl, C₇₋₆₀ alkylaryl, C₇₋₆₀ arylalkyl, (C₁₋₃₀ alkyl ether)₁₋₁₀₀, (C₇₋₆₀ alkylaryl ether)₁₋₁₀₀, (C₁₋₃₀ alkyl thioether)₁₋₁₀₀, (C₇₋₆₀ alkylaryl thioether)₁₋₁₀₀, (C₂₋₅₀ alkyl ester)₁₋₁₀₀, (C₈₋₇₀ alkylaryl ester)₁₋₁₀₀, -R-CO-O-(C₁₋₃₀ alkyl ether)₁₋₁₀₀, (C₄₋₅₀ alkyl urethane)₁₋₁₀₀, (C₁₀₋₈₀ alkylaryl urethane)₁₋₁₀₀, (C₅₋₅₀ alkyl urea)₁₋₁₀₀, (C₁₀₋₈₀ alkylaryl urea)₁₋₁₀₀, (C₂₋₅₀ alkyl amide)₁₋₁₀₀, (C₈₋₇₀ alkylaryl amide)₁₋₁₀₀, (C₃₋₃₀ alkyl anhydride)₁₋₁₀₀, (C₉₋₆₀ alkylaryl anhydride)₁₋₁₀₀, (C₂₋₃₀ alkyl carbonate)₁₋₁₀₀, (C₈₋₆₀ alkylaryl carbonate)₁₋₁₀₀, -R₁-O-CO-NH-(R₂ or Ph-R₂-Ph)-NH-CO-O-(C₁₋₃₀ alkyl ether or C₇₋₆₀ alkylaryl ether)₁₋₁₀₀, -R₁-O-CO-NH-(R₂ or Ph-R₂-Ph)-NH-CO-O-(C₂₋₅₀ alkyl ester or C₈₋₇₀ alkylaryl ester)₁₋₁₀₀, -R₁-O-CO-NH-(R₂ or Ph-R₂-Ph)-NH-CO-O-(C₁₋₃₀ alkyl ether or C₇₋₆₀ alkylaryl ether)₁₋₁₀₀-CO-NH-(R₂ or Ph-R₂-Ph)-NH-CO-O-, -R₁-

NH-CO-NH-(R₂ or Ph-R₂-Ph)-NH-CO-O-(C₁₋₃₀ alkyl ether or C₇₋₆₀ alkylaryl ether)₁₋₁₀₀, -R₁-NH-CO-NH-(R₂ or Ph-R₂-Ph)-NH-CO-O-(C₂₋₅₀ alkyl ester or C₈₋₇₀ alkylaryl ester)₁₋₁₀₀, -R₁-NH-CO-NH-(R₂ or Ph-R₂-Ph)-NH-CO-O-(C₁₋₃₀ alkyl ether or C₇₋₆₀ alkylaryl ether)₁₋₁₀₀, -CO-NH-(R₂ or Ph-R₂-Ph)-NH-CO-O-, -R₁-O-CO-NH-(R₂ or Ph-R₂-Ph)-NH-CO-NH-(C₂₋₅₀ alkyl amide or C₇₋₇₀ alkylaryl amide)₁₋₁₀₀, or -R₁-NH-CO-NH-(R₂ or Ph-R₂-Ph)-NH-CO-NH-(C₂₋₅₀ alkyl amide or C₇₋₇₀ alkylaryl amide)₁₋₁₀₀;

and each C is independently -R-, -R-Ph in which Ph is p-phenylene or a salt thereof.

4. A compound of formula I as claimed in any one of claims 1 to 3 wherein each D is independently -SO₃⁻, -OSO₃⁻, -CO₂⁻, -PO₃⁻, -O-PO₃²⁻, -O-PO(O⁻)-O-PO₃²⁻, -O-PO(O⁻)-O-PO(O⁻)-O-PO₃²⁻, -O-PO(O⁻)-O-CH₂-CH₂-NH₃⁺, or a salt thereof.

5. A compound of formula I as claimed in any one of claims 1 to 4 wherein m is 0, or a salt thereof.

6. A compound of formula I as claimed in any one of claims 1 to 5 wherein m is 0 and n is 4 to 16, or a salt thereof.

7. A compound of formula I as claimed in any one of claims 1 to 4 wherein m and n each have a value of up to 16 and the sum of m and n is 4 to 16, or a salt thereof.

8. A composition comprising a biologically compatible substance and a compound of formula I



wherein

F is a fullerene core;

each X is independently -CO₂⁻, -SO₃⁻, -OH, -SH, -PO₃⁻, -O-PO₃²⁻, -O-PO(O⁻)-O-PO₃²⁻, -O-PO(O⁻)-O-CH₂-CH₂-NH₃⁺, -NH₂, -NH₃⁺, -N⁺H₂R_a, -N⁺HR_aR_b or -N⁺R_aR_bR_c;

each Y is -A-B-, in which A is independently -CH₂-, -O-, -S-, -NH-CO-NH-, or -NH-CO-; and B is independently -R_d-O-[Si(CH₃)₂-O]₁₋₁₀₀, C₁₋₂₀₀₀ alkyl, C₆₋₄₀ aryl, C₇₋₆₀ alkylaryl, C₇₋₆₀ arylalkyl, (C₁₋₃₀ alkyl ether)₁₋₁₀₀, (C₆₋₄₀ aryl ether)₁₋₁₀₀, (C₇₋₆₀ alkylaryl ether)₁₋₁₀₀, (C₇₋₆₀ arylalkyl ether)₁₋₁₀₀, (C₁₋₃₀ alkyl thioether)₁₋₁₀₀, (C₆₋₄₀ aryl thioether)₁₋₁₀₀, (C₇₋₆₀ alkylaryl thioether)₁₋₁₀₀, (C₇₋₆₀ arylalkyl thioether)₁₋₁₀₀, (C₂₋₅₀ alkyl ester)₁₋₁₀₀, (C₇₋₆₀ aryl ester)₁₋₁₀₀, (C₈₋₇₀ alkylaryl ester)₁₋₁₀₀, (C₈₋₇₀ arylalkyl ester)₁₋₁₀₀, -R-CO-O-(C₁₋₃₀ alkyl ether)₁₋₁₀₀, -R-CO-O-(C₆₋₄₀ aryl ether)₁₋₁₀₀, -R-CO-O-(C₇₋₆₀ alkylaryl ether)₁₋₁₀₀, -R-CO-O-(C₇₋₆₀ arylalkyl ether)₁₋₁₀₀, (C₄₋₅₀ alkyl urethane)₁₋₁₀₀, (C₁₄₋₆₀ aryl urethane)₁₋₁₀₀, (C₁₀₋₈₀ alkylaryl urethane)₁₋₁₀₀, (C₁₀₋₈₀ arylalkyl urethane)₁₋₁₀₀, (C₅₋₅₀ alkyl urea)₁₋₁₀₀, (C₁₄₋₆₀ aryl urea)₁₋₁₀₀, (C₁₀₋₈₀ alkylaryl urea)₁₋₁₀₀, (C₁₀₋₈₀ arylalkyl urea)₁₋₁₀₀, (C₂₋₅₀ alkyl amide)₁₋₁₀₀, (C₇₋₆₀ aryl amide)₁₋₁₀₀, (C₈₋₇₀ alkylaryl amide)₁₋₁₀₀, (C₈₋₇₀ arylalkyl amide)₁₋₁₀₀, (C₃₋₃₀ alkyl anhydride)₁₋₁₀₀, (C₈₋₅₀ aryl anhydride)₁₋₁₀₀, (C₉₋₆₀ alkylaryl anhydride)₁₋₁₀₀, (C₉₋₆₀ arylalkyl anhydride)₁₋₁₀₀, (C₂₋₃₀ alkyl carbonate)₁₋₁₀₀, (C₇₋₅₀ aryl carbonate)₁₋₁₀₀, (C₈₋₆₀ alkylaryl carbonate)₁₋₁₀₀, (C₈₋₆₀ arylalkyl carbonate)₁₋₁₀₀, -R₁-O-CO-NH-(R₂ or Ar-R₂-Ar)-NH-CO-O-(C₁₋₃₀ alkyl ether, C₆₋₄₀ aryl ether, C₇₋₆₀ alkylaryl ether, or C₇₋₆₀ arylalkyl ether)₁₋₁₀₀, -R₁-O-CO-NH-(R₂ or Ar-R₂-Ar)-NH-CO-O-(C₂₋₅₀ alkyl ester, C₇₋₆₀ aryl ester, C₈₋₇₀ alkylaryl ester, or C₈₋₇₀ arylalkyl ester)₁₋₁₀₀, -R₁-O-CO-NH-(R₂ or Ar-R₂-Ar)-NH-CO-O-(C₁₋₃₀ alkyl ether, C₆₋₄₀ aryl ether, C₇₋₆₀ alkylaryl ether, or C₇₋₆₀ arylalkyl ether)₁₋₁₀₀-CO-NH-(R₂ or Ar-R₂-Ar)-NH-CO-O-, -R₁-O-CO-NH-(R₂ or Ar-R₂-Ar)-NH-CO-O-(C₂₋₅₀ alkyl ester, C₇₋₆₀ aryl ester, C₈₋₇₀ alkylaryl ester, or C₈₋₇₀ arylalkyl ester)₁₋₁₀₀-R₃-O-CO-NH-(R₂ or Ar-R₂-Ar)-NH-CO-O-, -R₁-NH-CO-NH-(R₂ or Ar-R₂-Ar)-NH-CO-O-(C₁₋₃₀ alkyl ether, C₆₋₄₀ aryl ether, C₇₋₆₀ alkylaryl ether, or C₇₋₆₀ arylalkyl ether)₁₋₁₀₀, -R₁-NH-CO-NH-(R₂ or Ar-R₂-Ar)-NH-CO-O-(C₂₋₅₀ alkyl ester, C₇₋₆₀ aryl ester, C₈₋₇₀ alkylaryl ester, or C₈₋₇₀ arylalkyl ester)₁₋₁₀₀, -R₁-NH-CO-NH-(R₂ or Ar-R₂-Ar)-NH-CO-O-(C₁₋₃₀ alkyl ether, C₆₋₄₀ aryl ether, C₇₋₆₀ alkylaryl ether, or C₇₋₆₀ arylalkyl ether)₁₋₁₀₀-CO-NH-(R₂ or Ar-R₂-Ar)-NH-CO-O-, -R₁-NH-CO-NH-(R₂ or Ar-R₂-Ar)-NH-CO-O-(C₂₋₅₀ alkyl ester, C₇₋₆₀ aryl ester, C₈₋₇₀ alkylaryl ester, or C₈₋₇₀ arylalkyl ester)₁₋₁₀₀-R₃-O-CO-NH-(R₂ or Ar-R₂-Ar)-NH-CO-O-, -R₁-O-CO-NH-(R₂ or Ar-R₂-Ar)-NH-CO-NH-(C₂₋₅₀ alkyl amide, C₇₋₆₀ aryl amide, C₈₋₇₀ alkylaryl amide, or C₈₋₇₀ arylalkyl amide)₁₋₁₀₀, or -R₁-NH-CO-NH-(R₂ or Ar-R₂-Ar)-NH-CO-NH-(C₂₋₅₀ alkyl amide, C₇₋₆₀ aryl amide, C₇₋₇₀ alkylaryl amide, or C₇₋₇₀ arylalkyl amide)₁₋₁₀₀;

each Z is -C-D, wherein C is independently -R-, -R-Ar-, -Ar-, or -Ar-R-; and D is independently -OH, -SH, -SO₃⁻, -OSO₃⁻, -CO₂⁻, -PO₃⁻, -O-PO₃²⁻, -O-PO(O⁻)-O-PO₃²⁻, -O-PO(O⁻)-O-PO(O⁻)-O-PO₃²⁻, -O-PO(O⁻)-O-CH₂-CH₂-NH₃⁺, -NH₂, -NH₃⁺, -N⁺H₂R_a, -N⁺HR_aR_b or -N⁺R_aR_bR_c; and

m is 0-30, n is 0-30 and the sum of m and n is 2-30;

in which each of R, R₁, R₂, R₃, R_a, R_b, R_c, R_d, R_a, R_b, and R_c is independently C₁₋₂₀ alkyl, and Ar is independently C₆₋₄₀ aryl, or a salt thereof.

9. A composition as claimed in claim 8 wherein in the compound of formula I

each B is independently -R_d-O-[Si(CH₃)₂-O]₁₋₁₀₀, C₁₋₂₀₀₀ alkyl, C₆₋₄₀ aryl, C₇₋₆₀ alkylaryl, C₇₋₆₀ arylalkyl, (C₁₋₃₀ alkyl ether)₁₋₁₀₀, (C₇₋₆₀ alkylaryl ether)₁₋₁₀₀, (C₁₋₃₀ alkyl thioether)₁₋₁₀₀, (C₇₋₆₀ alkylaryl thioether)₁₋₁₀₀, (C₂₋₅₀ alkyl ester)₁₋₁₀₀, (C₈₋₇₀ alkylaryl ester)₁₋₁₀₀, -R-CO-O-(C₁₋₃₀ alkyl ether)₁₋₁₀₀, (C₄₋₅₀ alkyl urethane)₁₋₁₀₀, (C₁₀₋₈₀ alkylaryl urethane)₁₋₁₀₀, (C₅₋₅₀ alkyl urea)₁₋₁₀₀, (C₁₀₋₈₀ alkylaryl urea)₁₋₁₀₀, (C₂₋₅₀ alkyl amide)₁₋₁₀₀, (C₈₋₇₀ alkylaryl amide)₁₋₁₀₀, (C₃₋₃₀ alkyl anhydride)₁₋₁₀₀, (C₉₋₆₀ alkylaryl anhydride)₁₋₁₀₀, (C₂₋₃₀ alkyl carbonate)₁₋₁₀₀, (C₈₋₆₀ alkylaryl carbonate)₁₋₁₀₀, -R₁-O-CO-NH-(R₂ or Ph-R₂-Ph)-NH-CO-O-(C₁₋₃₀ alkyl ether or C₇₋₆₀ alkylaryl ether)₁₋₁₀₀, -R₁-O-CO-NH-(R₂ or Ph-R₂-Ph)-NH-CO-O-(C₂₋₅₀ alkyl ester or C₈₋₇₀ alkylaryl ester)₁₋₁₀₀, -R₁-O-CO-NH-(R₂ or Ph-R₂-Ph)-NH-CO-O-(C₁₋₃₀ alkyl ether or C₇₋₆₀ alkylaryl ether)₁₋₁₀₀-CO-NH-(R₂ or Ph-R₂-Ph)-NH-CO-O-, -R₁-NH-CO-NH-(R₂ or Ph-R₂-Ph)-NH-CO-O-(C₁₋₃₀ alkyl ether or C₇₋₆₀ alkylaryl ether)₁₋₁₀₀, -R₁-NH-CO-NH-(R₂ or Ph-R₂-Ph)-NH-CO-O-(C₂₋₅₀ alkyl ester or C₈₋₇₀ alkylaryl ester)₁₋₁₀₀, -R₁-NH-CO-NH-(R₂ or Ph-R₂-Ph)-NH-CO-O-(C₁₋₃₀ alkyl ether or C₇₋₆₀ alkylaryl ether)₁₋₁₀₀, -CO-NH-(R₂ or Ph-R₂-Ph)-NH-CO-O-, -R₁-O-CO-NH-(R₂ or Ph-R₂-Ph)-NH-CO-NH-(C₂₋₅₀ alkyl amide or C₇₋₇₀ alkylaryl amide)₁₋₁₀₀, or -R₁-NH-CO-NH-(R₂ or Ph-R₂-Ph)-NH-CO-NH-(C₂₋₅₀ alkyl amide or C₇₋₇₀ alkylaryl amide)₁₋₁₀₀;

and each C is independently -R-, -R-Ph in which Ph is p-phenylene or a salt thereof.

10. A composition as claimed in either one of claims 8 and 9 wherein in the compound of formula I
each X is independently -CO₂⁻, -SO₃⁻, -SH, -PO₃⁻, -O-PO₃²⁻, -O-PO(O⁻)-O-PO₃²⁻, -O-PO(O⁻)-O-PO(O⁻)-O-PO₃²⁻, -O-PO(O⁻)-O-CH₂-CH₂-NH₃⁺, or a salt thereof.
11. A composition as claimed in any one of claims 8 to 10 wherein in the compound of formula I
each D is independently -SO₃⁻, -OSO₃⁻, -CO₂⁻, -PO₃⁻, -O-PO₃²⁻, -O-PO(O⁻)-O-PO₃²⁻, -O-PO(O⁻)-O-PO(O⁻)-O-PO₃²⁻, -O-PO(O⁻)-O-CH₂-CH₂-NH₃⁺, or a salt thereof.
12. A composition as claimed in any one of claims 8 to 11 wherein in the compound of formula I, m is 0-16, n is 1-16, and the sum of m and n is 4-16.
13. A composition as claimed in claim 8 containing a compound or salt as claimed in any one of claims 1 to 7.
14. A compound of formula I as defined in claim 8 or a salt thereof, for medical use.
15. The use of a compound of formula I as defined in claim 8 or a salt thereof, for the manufacture of a medicament for the treatment of disorders or diseases associated with free radicals.

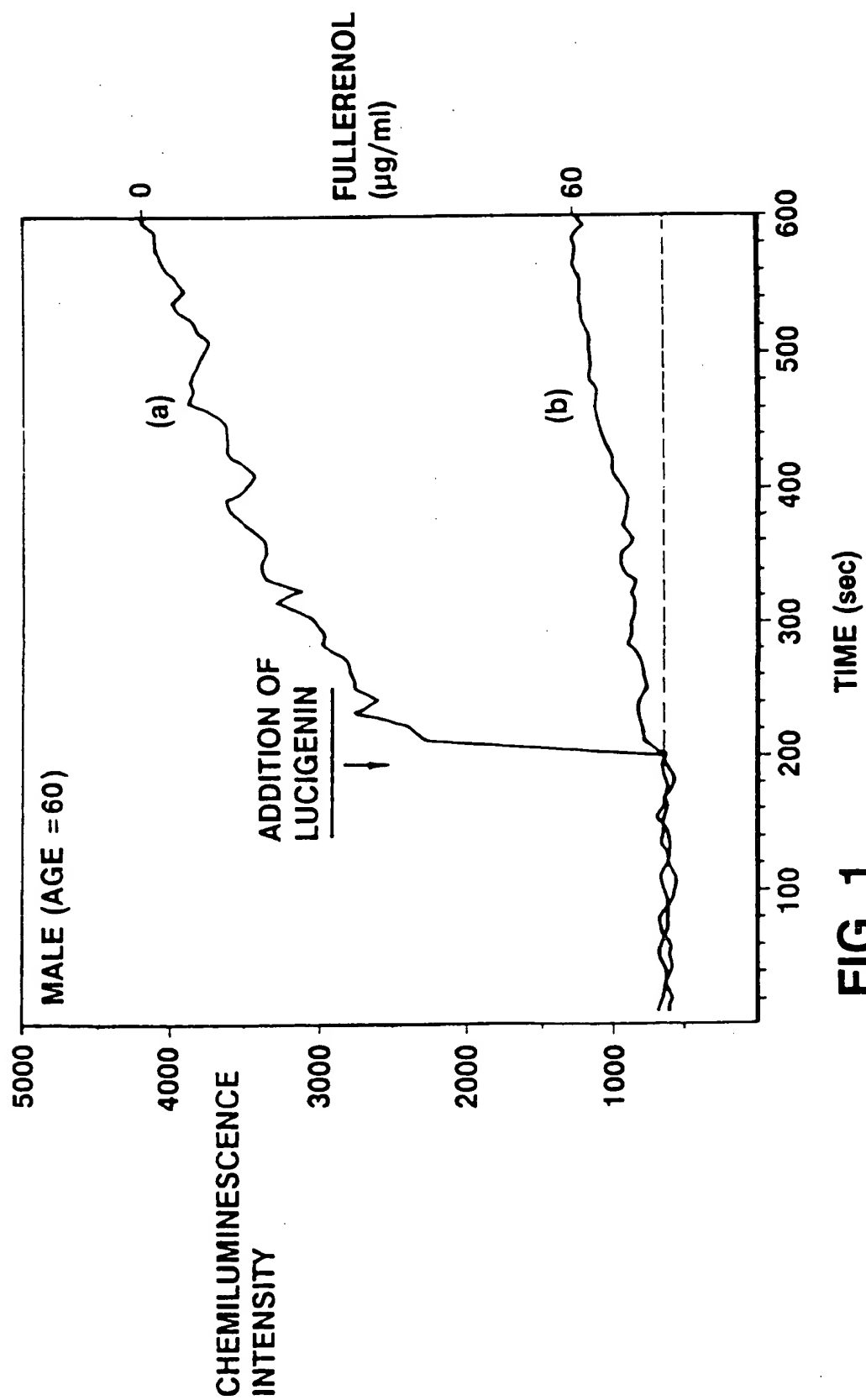


FIG. 1

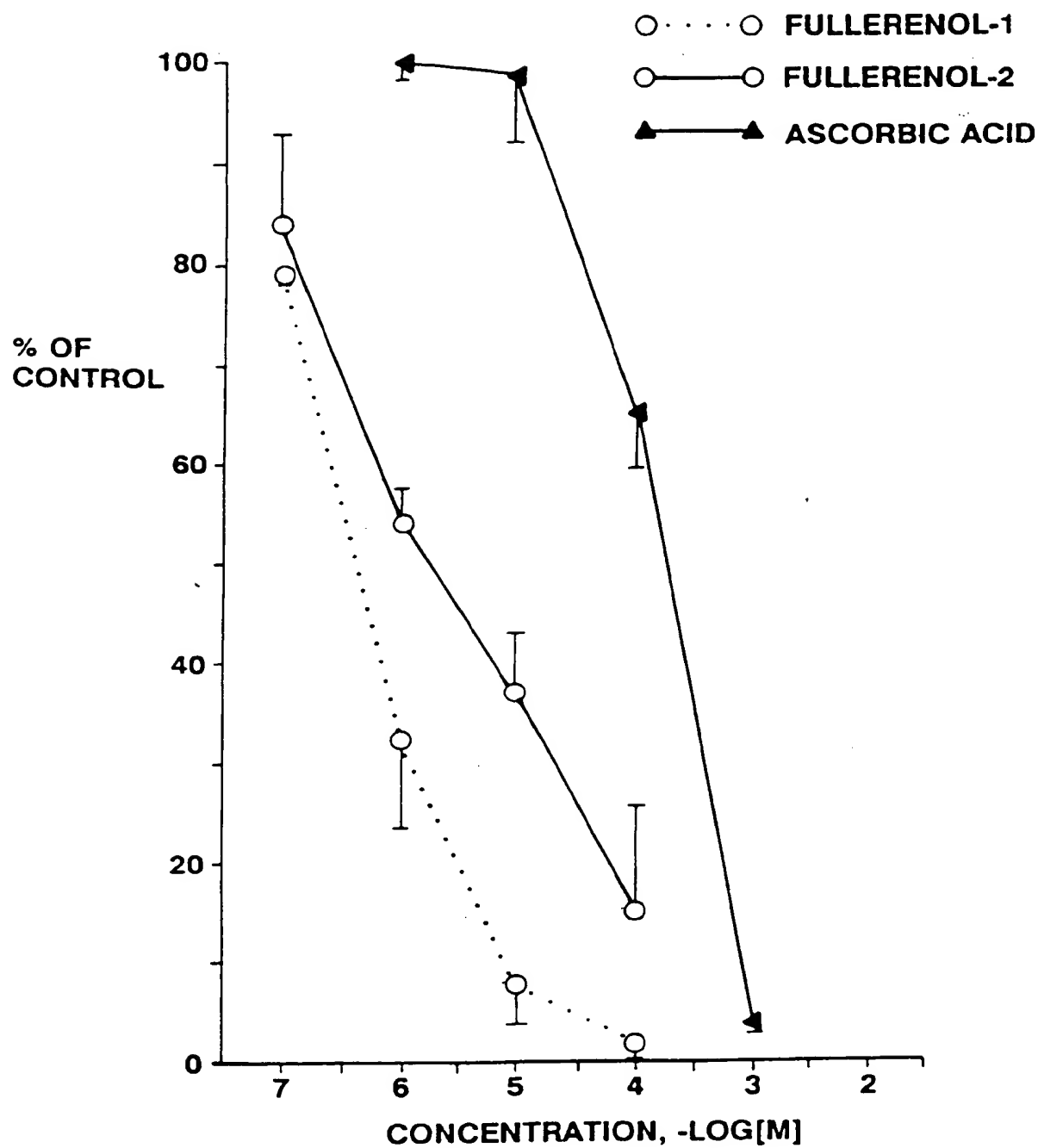


FIG. 2



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EUROPEAN SEARCH REPORT

Application Number
EP 96 30 2581

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The present search report has been drawn up for all claims			TECHNICAL FIELDS SEARCHED (Int.Cl.6)
			C01B
Place of search		Date of completion of the search	Examiner
BERLIN		27 September 1996	Clement, J-P
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons --- A : member of the same patent family, corresponding document	

EPO FORM 1501 03/92 (P04C01)



European Patent
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EUROPEAN SEARCH REPORT

Application Number
EP 96 30 2581

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		<p>CLASSIFICATION OF THE APPLICATION (Int.Cl.6)</p>
		<p>TECHNICAL FIELDS SEARCHED (Int.Cl.6)</p>
<p>The present search report has been drawn up for all claims</p>		
Place of search	Date of completion of the search	Examiner
BERLIN	27 September 1996	Clement, J-P
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons</p> <p>----- & : member of the same patent family, corresponding document</p>		

EPO FORM 1503 01.92 (P04C01)